

Delta-5-desaturase: A novel therapeutic target for cancer management

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ABSTRACT

Delta-5 desaturase (D5D) is a rate-limiting enzyme that introduces double-bonds to the delta-5 position of the n-3 and n-6 polyunsaturated fatty acid chain. Since fatty acid metabolism is a vital factor in cancer development, several recent studies have revealed that D5D activity and expression could be an independent prognostic factor in cancers. However, the mechanistic basis of D5D in cancer progression is still controversial. The classical concept believes that D5D could aggravate cancer progression via mediating arachidonic acid (AA)/prostaglandin E₂ production from dihomo- γ -linolenic acid (DGLA), resulting in activation of EP receptors, inflammatory pathways, and immunosuppression. On the contrary, D5D may prevent cancer progression through activating ferroptosis, which is iron-dependent cell death. Suppression of D5D by RNA interference and small-molecule inhibitor has been identified as a promising anti-cancer strategy. Inhibition of D5D could shift DGLA peroxidation pattern from generating AA to a distinct anti-cancer free radical byproduct, 8-hydroxyoctanoic acid, resulting in activation of apoptosis pathway and simultaneously suppression of cancer cell survival, proliferation, migration, and invasion. Hence, understanding the molecular mechanisms of D5D on cancer may therefore facilitate the development of novel therapeutical applications. Given that D5D may serve as a promising target in cancer, in this review, we provide an updated summary of current knowledge on the role of D5D in cancer development and potentially useful therapeutic strategies.

Introduction

Delta-5 desaturase (D5D) is a rate-limiting enzyme in polyunsaturated fatty acids (PUFAs) synthesis for introducing double-bonds to the delta-5 position in the fatty acid chain [1]. Given the key role of the PUFAs synthesis pathway in energy homeostasis, D5D has been widely studied in metabolic diseases, such as hepatic steatosis and type 2 diabetes [2,3]. The two main functions of D5D are (1) to catalyze eicosatetraenoic acid (ETA) to eicosapentaenoic acid (EPA) in the n-3 PUFAs pathway, and (2) to catalyze dihomo- γ -linolenic acid (DGLA) to arachidonic acid (AA) in the n-6 PUFAs pathway [1]. Although the effect of the n-3 PUFAs pathway on cancer has been widely studied, the

function of the n-6 PUFAs pathway, especially D5D, on cancer has remained poorly understood. However, recent studies have revealed that D5D may also play a crucial role in cancer by regulating inflammation, ferroptosis, apoptosis, proliferation, and metastasis [4–7]. Therefore, it is critical to find out how D5D participates in diverse mechanisms so researchers can develop new therapeutical strategies with the proper fatty acids supplementation and fulfill the promise of precision medicine.

The structure, distribution, and function of D5D

D5D is coded by the *FADS1* gene, which is located on chromosome

Abbreviations: PUFAs, polyunsaturated fatty acids; D5D, delta-5-desaturase; DGLA, dihomo- γ -linolenic acid; COX-2, cyclooxygenase-2; PGs, prostaglandins; PGE₂, prostaglandin E₂; AA, arachidonic acid; ETA, eicosatetraenoic acid; EPA, eicosapentaenoic acid; EDA, eicosadienoic acid; SNP, single-nucleotide acid polymorphism; ER, endoplasmic reticulum; 8-HOA, 8-hydroxyoctanoic acid; RNAi, RNA interference; HDAC, histone deacetylases; TCGA, the cancer genome atlas; LTs, leukotrienes; LXR, liver X receptor; PPAR α , peroxisome proliferator-activated receptor α ; RXR, retinoid X receptor; SREBP-1c, sterol regulatory element-binding protein 1c; 5-LOX, 5-lipoxygenase; EMT, epithelial-mesenchymal transition; MDSCs, myeloid-derived suppressor cells; DNMT3B, DNA methyltransferase 3B; ROS, reactive oxygen species; YAP1, yes-associated protein-1; TAZ, transcriptional coactivator with PDZ-binding motif; TME, tumor microenvironment; Bax, Bcl-2-associated X protein; MMP, matrix metalloproteinase; GPX4, glutathione peroxidase 4; ELOVL5, elongation of very long-chain fatty acid protein 5; POBN, α -(4-pyridyl 1-oxide)-N-tert-butylnitrene; 5-FU, fluorouracil; EpCAM, epithelial cell adhesion molecule; 3WJ, 3-way junction; HAT, histone acetyltransferase.

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11q12-13.1 [8]. *FADS1* and other subtypes of *FADS* genes consist of 11 introns and 12 exons and occupy 100 kb regions in total. The variants of the *FADS* gene cluster have been reported to be closely associated with fatty acid consumption, pregnancy, auto-immune diseases, and cancers. D5D is a typical front-end fatty acyl-CoA desaturase, which binds to the endoplasmic reticulum (ER) membrane and catalyzes the synthesis of downstream PUFAs. The D5D enzyme belongs to the superfamily of iron-dependent enzymes that consists of two domains, cytochrome b5 domain at N-terminal with heme-binding motifs and desaturase domain at C-terminal with histidine boxes where one of the histidine residuals is replaced by glutamine, which is responsible for the activity of desaturase. The replacement of the glutamine back to histidine (or isoleucine) could result in abrogating the desaturase's activity [1,9]. However, the precise crystal structure of D5D is still unclear as it is difficult to stabilize the membrane-bound enzyme with full activities [10]. Since the D5D and D6D shared many similarities in gene SNP, protein structure, and function, it could be a challenge to isolate enzymes exclusively exhibiting D5D activity on their substrates (DGLA and ETA) rather than catalyzing on broad PUFAs' precursors.

Fatty acid desaturases are widely distributed in most animal tissues, and are essential to synthesize PUFAs for energy supply and signal transduction (serve as first/second messengers). The D5D enzyme is highly expressed in the brain, lung, pancreas, liver (highest), and variety of cancer cells [1]. The low D5D activity in serum lipids has been identified as a potential biomarker in the prediction of disease status, such as metabolic risk in children, hepatic steatosis, type 2 diabetes, and cancers [3,11–13]. A recent The Cancer Genome Atlas (TCGA) database analysis has indicated that the mRNA expression levels of *FADS1* are increased in head-neck squamous cell carcinoma tissues [14].

D5D in the n-3/-6 PUFAs pathway is responsible to convert dietary essential fatty acids (α -linolenic acid and linolenic acid) to a series of downstream PUFAs by introducing double-bonds to the fatty acid chain from the carboxylic end, increasing unsaturation (Fig. 1). Another type of desaturase catalyzing PUFAs synthesis from methyl-end to pre-existing double bonds, such as D12D and D15D, are not present in humans/mammals. Therefore, mammals have to uptake α -linolenic acid and linoleic acid from their daily diet to maintain the balance of fatty acid compositions. Saturated fatty acids have a higher transition temperature than unsaturated fatty acids. Therefore, the ratio of saturated to unsaturated fatty acid is considered as the primary determinant of the melting temperature of triglycerides for regulating cellular membrane fluidity [1,10,15]. In our daily diet, α -linolenic acid and linoleic acid are the major resource of n-3 and n-6 fatty acids, respectively [16]. Both n-6/-3 fatty acid synthesis pathways share the same set of enzymes, including D6D, elongase, and D5D, of which D5D is in response to catalyze the formation of EPA in the n-3 pathway and AA in the n-6 pathway [8].

D5D implication in PUFA related diseases including cancer

EPA and AA are the precursors of a variety of inflammatory mediators, such as prostaglandins (PGs) and leukotrienes (LTs), for regulating physiological and pathological functions [17]. Selective knocking down *FADS1* by *in vivo* antisense oligonucleotide could induce hepatic inflammation and atherosclerosis in mice [18,19]. *In vitro* study have further confirmed that the knockdown of *FADS1* activates classic M1 macrophages and inhibits M2 activation, and causes alterations of liver X receptor (LXR) associated gene expression, implicating the key role of D5D in liver lipid metabolism [19]. Additionally, a population-based Kuopio Ischaemic Heart Disease Risk Factor Study has suggested that higher D5D activity is favorably associated with stroke and metabolic risk factors, including low systolic/diastolic blood pressure, insulin level, C-reactive protein concentrations, BMI, and better homeostatic model assessment indices [20]. Additionally, high DGLA concentration and low D5D activity are valuable predictors of hepatic steatosis [2]. D5D also has been identified as a risk factor of type 2 diabetes. The level of plasma apoB is negatively correlated with D5D activity [3]. Moreover, the D5D activity is also negatively associated with serum triiodothyronine in adolescents with eating disorders, indicating that D5D may participate in thyroid hormone regulation [21].

Several rodent studies have reported that the expression and activity of D5D could be influenced by diet. Indeed, the PUFAs synthesis is regulated under a strong feedback pathway [1]. The D5D is inhibited by dietary PUFAs, especially the high-fat diet [22]. Different transcription factors, including peroxisome proliferator-activated receptor α (PPAR α), retinoid X receptor (RXR), sterol regulatory element-binding protein 1c (SREBP-1c), have been reported with a strong regulator effect on D5D expression [1]. All three desaturases, D5D, D6D, and D9D, can be activated by SREBP-1c via regulating mRNA expression. It has been observed that mice with overexpression of SREBP-1a, -1c, and -2 have higher expression of hepatic D5D than the wild-type mouse. After a fast/fed cycle, supplementation of a carbohydrate diet with linoleate or EPA significantly inhibits D5D expression, indicating that PUFAs could trigger the feedback suppression of D5D [23]. Another transcription factor PPAR α controls β -oxidation in the liver [1]. Activation of PPAR α could induce D5D expression in fast conditions. The cross-talk between SREBP-1c and PPAR α may build the basic mechanism of how D5D is regulated under different nutritional statuses and energy states [18,23]. A recent study based on UK Biobank has revealed the positive association between *FADS1* with rs174561 variant in the frontal cortex and daytime napping. Moreover, two-sample Mendelian randomization analyses have confirmed that more frequent daytime napping is correlating to independent risk factors (waist circumference and blood pressure) of cardiometabolic diseases [24]. Given the fact that many downstream inflammatory mediators are generated by the D5D-catalyzed n-6 PUFAs pathway, the correlation between daytime napping and cardiometabolic

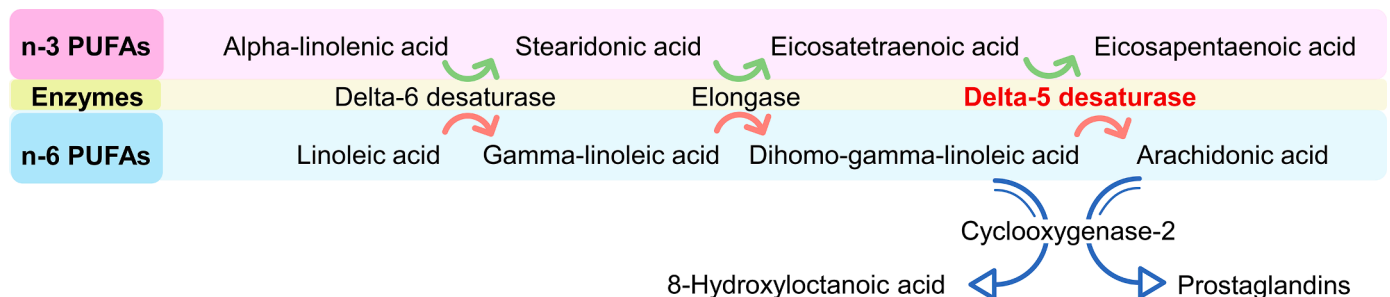


Fig. 1. Pathway of n-3 and n-6 polyunsaturated fatty acids (PUFAs) synthesis. The n-3 PUFAs, such as Alpha-linolenic acid is metabolized by delta-6-desaturase and elongase to Eicosatetraenoic acid, which further peroxidized by Delta-5-Desaturase to Eicosapentaenoic acid (Shown in red row). The same sets of enzymes metabolize n-6 PUFAs, linoleic acid, to Arachidonic acid (n-6 metabolism shown in blue). The COX-2 is responsible for conversion of arachidonic acid to precancerous prostaglandins, whereas COX-2 is also involved in peroxidation of Dihomo-gamma-linoleic acid to an anti-cancer compound, 8-HOA (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

risks may be explained by activation of AA/PGs-mediated inflammatory response. Of note, the data of this study has been collected from individuals living in the United Kingdom where the Western diet is the mainstream. However, the D5D expression and activity may vary in patients with different diets and PUFAs uptake. For example, an iron-rich diet could decrease D5D activity but increase D5D mRNA expression in male Wistar rats [25]. A comparative study compares the D5D gene expression between Europeans and Chinese. It has been found that Europeans with high saturated fatty acid and less PUFAs' diet express higher D5D genes in peripheral blood mononuclear cells, indicating the strong correlation between dietary fatty acid uptake and D5D activity [22]. Therefore, the relationship between daytime napping, D5D expression/activity, and diet may need to be investigated in more populations with different dietary preferences.

More studies recently have revealed the potential correlation between D5D expression and cancer [13,26,27]. Given the key role of inflammation in cancer, the D5D may be involved in carcinogenesis via mediating PUFAs metabolism in the tumor microenvironment. However, the correlation between D5D and cancer development is still controversial (Table 1). Studies have suggested that a low D5D level is a predictor of worse prognosis in non-small cell lung cancer and esophageal squamous cell carcinoma. Patients with low *FADS1* expression appear poor overall survival and disease-free survival [27,28]. On the contrary, other studies have demonstrated that high expression of D5D is an indicator of cancer progression. A recent TCGA based study has suggested that bladder cancer patients with high *FADS1* expression have a poor prognosis [26]. The *in vitro* study further shows that over-expression of *FADS1* could lead to bladder cancer proliferation, whereas the *FADS1* knockdown could arrest the cell cycle [13]. Moreover, *FADS1* could be upregulated by a long non-coding RNA linc00460 in osteosarcoma, resulting in distant metastasis and reduced overall survival [29]. A genome-wide association study (GWAS) of colorectal cancer in East Asians has demonstrated that *FADS1* expression in colon tumor tissues is higher than normal tissues [30]. Additionally, *FADS1* is also upregulated in patients with hepatocellular carcinoma [31]. Why the opposite conclusions have been made in the above-listed studies? One possible explanation is that the function of D5D may vary in different organs and cancers. Although D5D is a critical enzyme for the synthesis of PUFAs, other enzymes, such as D6D, cyclooxygenase (COX),

5-lipoxygenase (5-LOX), need to be coupled with D5D to generate corresponding eicosanoids [17]. The function of D5D in cancer may be influenced by the status of other enzymes [32]. Diet and uptake of PUFAs could be another reason. For instance, the negative correlations of *FADS1* with lung cancer and esophageal squamous cell carcinoma have been established by analyzing tumor samples from patients in the same region [27,28]. Given the fact that D5D expression and activity could be regulated by diet, the interrelationships and relevance of D5D to cancer development may vary in patients from different regions with disparate food and PUFAs preferences. Therefore, more studies may need to be conducted to further validating the function of D5D in cancer in larger populations across different regions. Moreover, not only *FADS1* expression, but also certain SNPs of *FADS1*, such as rs174549, rs174548, and rs174550 have been identified as independent and favorable factors in predicting oral, lung, colorectal cancers, and laryngeal squamous cell carcinoma progression [33–36].

D5D regulates cancer progression via mediating prostaglandin E₂ (PGE₂) production

The role of fatty acid metabolism in cancer has been extensively studied as fatty acids could serve as an alternative fuel for providing energy to support cancer cell growth and proliferation [45]. However, fatty acids also contribute to tumorigenesis by mediating various signaling pathways. D5D is a rate-limiting enzyme for catalyzing the formation of AA/EPA from DGLA/ETA [8]. The newly formed AA could be continuously transformed to PGE₂ by COX-2 and PGE synthase in cancer cells [17]. As the most abundant prostaglandin, PGE₂ is involved in many aspects of tumorigenesis [46]. COX-2/PGE₂ axis contributes to the formation of the inflammatory microenvironment in the tumor tissues, resulting in proliferation, invasion, epithelial-mesenchymal transition (EMT), cancer cell stemness, and inhibition of apoptosis via regulating the function of macrophages, cancer-associated fibroblasts, CD8⁺ T cells, and myeloid-derived suppressor cells (MDSCs) (Fig. 2) [39–46,48–51]. Given the vital role of inflammation in cancer, the over-activation of the COX-2/PGE₂ pathway could upregulate the protein expression of phospho- NF-κB p65, resulting in invasion and proliferation in ovarian cancer cells [54]. In breast cancer cells, DNA methyltransferase 3B (DNMT3B) can be induced by PGE₂, leading to a

Table 1
Potential prognostic and/or predictive utility of D5D and its partners in cancers.

Molecules	Cancer type	Clinical outcomes	Prognostic/ predictive utility	Ref.
D5D	Non-small-cell lung cancer	(1) Higher expression in normal bronchial mucosa than tumor tissues (2) Negatively associates with tumor size and histological grade (3) Lower expression associates with shorter overall survival and disease-free survival	Protective	[27]
D5D	Esophageal squamous cell carcinoma	Associates with better disease-free survival and overall survival	Protective	[28]
D5D	Bladder cancer	(1) Positively associates with tumor grade (2) Enhances the proliferation	Poor prognosis	[13]
D5D	Laryngeal squamous cell carcinoma	High expression and bioactivity in tumor tissues	Undetermined	[14]
D5D	Oral cancer	Correlates to a decreased risk of oral cancer	Protective	[37]
rs174549				
D5D	Lung cancer	(1) Smoking-independent (2) Particularly associates with lung cancer in women	Undetermined	[34]
rs174548				
COX-2	Hypopharyngeal carcinoma	Associates with chemoresistant	Undetermined	[38]
COX-2	Colorectal cancer	Relates to susceptibility to cancer in Caucasians	Increased risk	[39]
COX-2	Osteosarcoma	(1) Higher expression in osteosarcoma than benign osteochondroma (2) Associates with tumor grade, clinical stage, and metastasis	Poor prognosis	[40]
COX-2	Breast cancer	High expression associates with poor overall survival	Poor prognosis	[41]
COX-2	Head and neck cancer	(1) Highly associates with a high risk of lymph node metastasis and advanced TNM stage (2) Poor survival effect	Poor prognosis	[42]
Linc00460	Osteosarcoma	Positively correlates with distant metastasis and poor overall survival	Poor prognosis	[29]
AA	Colorectal cancer	Positively associates with colorectal cancer	Increased risk	[43]
PGE ₂	Gastric cancer	PGE-M (a urinary metabolite of PGE ₂) is associated with a higher risk of gastric cancer	Increased risk	[44]

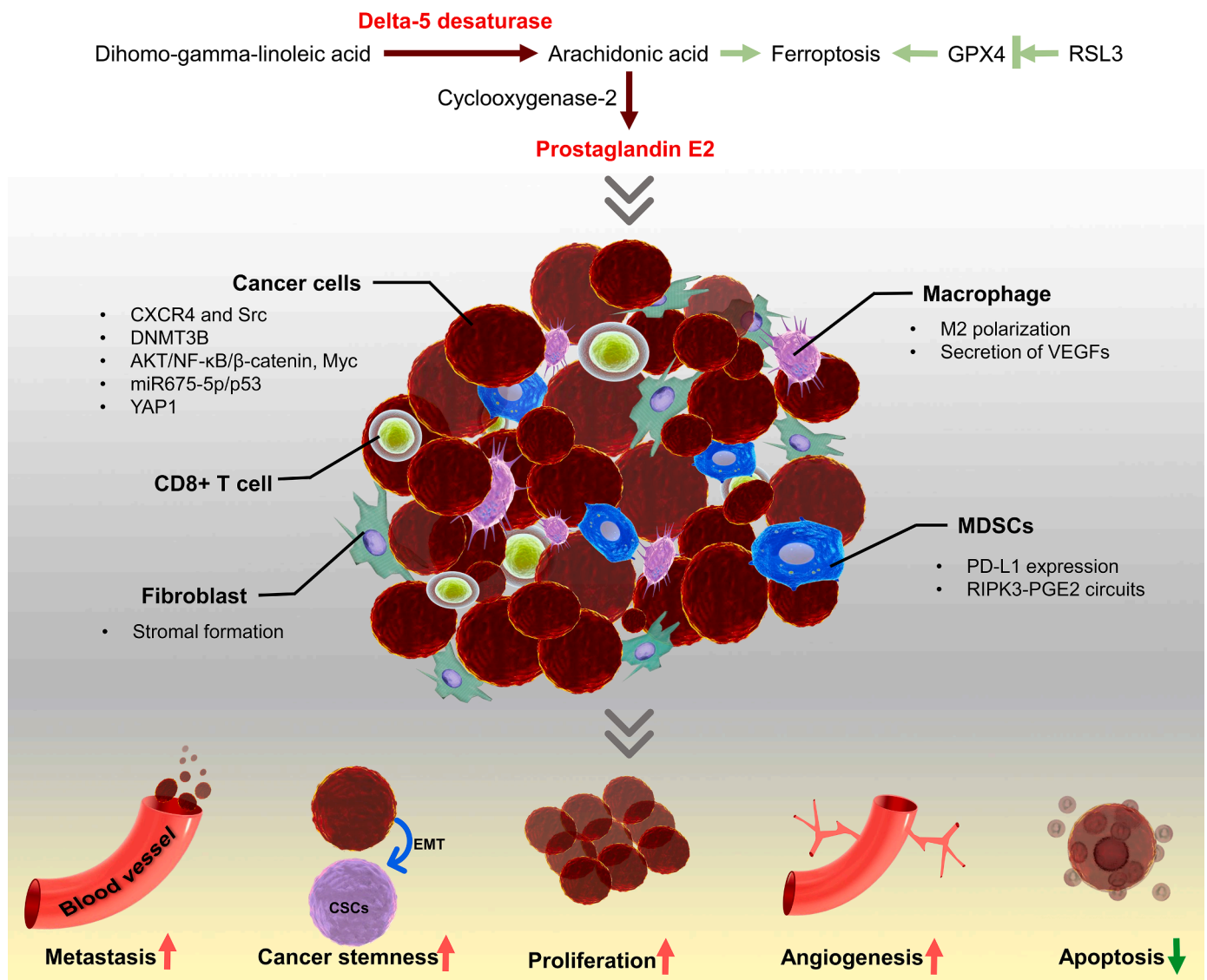


Fig. 2. Delta-5 desaturase (D5D) regulates cancer progression via mediating arachidonic acid (AA) and prostaglandin E2 (PGE₂) production. DGLA/AA/PGE₂ axis promotes cancer progression via increasing metastasis, cancer stemness, proliferation, angiogenesis, and decreasing apoptosis as shown in red and green arrows (bottom panel in the figure). The light green arrows indicate the role of DGLA and AA in ferroptosis (upper panel in the figure) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

significant epigenetic change in tumors and metastatic sites [55]. Tumor growth and migration are also depending on angiogenesis for transporting nutrients and chemical signals. The activation of PGE₂-EP2/4 could promote angiogenesis through CXCR4 and upregulation of Src [56,57]. Additionally, Orai1 has recently been identified as one of the downstream molecules of the EP4/PI3K pathway, which is responding to PGE₂-induced cancer cell migration [58]. The increased PGE₂ in cancer cells could further trigger a positive activation loop of YAP1/COX-2/EP4, resulting in colorectal cancer cell proliferation and polyp formation [59]. Not only inhibition of the immune system, but also a recent study has revealed that PGE₂ could promote colorectal progression by upregulation of miRNA 675-5p (miR675-5p) [60]. Additionally, other miRNAs and molecules, such as miR-370-3p, miR-206, miR-146a, syntenin-1 also could regulate PGE₂ production and inactivation in colorectal cancer [61–63].

Despite the importance of PGE₂ synthesis in cancer, the interrelationships and relevance of D5D expression and activity in PGE₂-mediated cancer progression remain poorly understood. One reason is that compared to D5D, COX-2 is a more conspicuous and accessible

target for regulating PGE₂ production, because the structure and function of COX-2 have been widely studied. Many studies have demonstrated the effect and mechanism of COX-2 inhibitors on various types of cancers *in vitro* and *in vivo*. However, long-term and high-dose treatment of COX-2 inhibitor is required to boost the PGE₂ inhibition in clinical practices [64,65]. Worth noting, not only in cancer cells but also COX-2 is the key molecule regulating inflammation and other physiological function throughout the body. Thus, the usage of COX-2 inhibitors in cancer treatment may raise safety concerns. Indeed, a significant increase in cardiovascular side effects has been observed in the clinical study when cancer patients received the addition of COX-2 inhibitors in the standard treatment [66]. Moreover, another study has suggested that COX-2 inhibitors fail to improve the overall and progression-free survival in cancer patients irrespective of COX-2 expression in tumors [67]. Therefore, continued research into upstream molecules of COX-2/PGE₂ pathways, such as D5D could help us to better understand the role of fatty acid metabolism in cancer progression and to overcome the limitation of COX-2 inhibitors.

D5D regulates cancer progression through activating ferroptosis

Ferroptosis is the iron-dependent mechanism of cell death and is affected by cellular redox status [68,69]. Although ferroptosis shared many biochemically and morphologically features with necrosis, such as chromatin condensation, cytoplasmic swelling, and damage of plasma membrane integrity, investigators believe that ferroptosis is a distinct cell death pathway differing from necrosis, apoptosis, and autophagy [69–72]. Compare to other cell death mechanisms, ferroptosis is featured by lipid peroxidation and iron accumulation. It has been found that iron metabolism, especially cellular iron versus systemic iron level, plays a key role in ferroptosis [68]. Iron could promote ferroptosis by inducing reactive oxygen species (ROS) generation via Fenton reaction or increasing the activity of prolyl hydroxylase and lipoxygenase [68]. Additionally, products derived from PUFAs peroxidation, such as hydroperoxides and 4-hydroxynonenal may also lead to ferroptotic cell death [73]. Among all the non-oxygenated phospholipid species, doubly and triply oxygenated AA and adrenic acid-containing phosphatidylethanolamine species are the most important phospholipids in the ferroptosis pathway [74]. The generation of these derivatives during ferroptosis requires the function of two genes, *ACSL4* and *LPCAT3* [70, 74–76]. Notably, a recent study has suggested that DGLA (precursor of AA) may lead to ferroptosis in cancer cells [77]. It has been observed that the DGLA-induced cancer cell death could be blocked by Ferrostatin-1, which is a selective inhibitor of ferroptosis, indicating that DGLA is a ferroptosis inducer [77]. Since D5D is the primary enzyme for AA production from DGLA, it is plausible that D5D plays a key role in ferroptosis. D5D expression and activity may affect the ferroptosis pathway via regulating the content of n-3/n-6 PUFAs in cancer cells.

Studies have demonstrated that induction of ferroptosis could inhibit cancer development and enhance the efficacy of chemotherapy, targeted therapy, and radiotherapy [78]. The role of D5D and lipid peroxidation in ferroptosis has been recently explored in cancer cells. The differential expression of D5D has been observed between intestinal-type and mesenchymal-type gastric cancer cells. By knocking out the D5D gene or using small molecule D5D inhibitor CP-24879, researchers have demonstrated that the expression and activity of D5D are positively correlated with the ferroptosis sensitivity of gastric cancer cells. Indeed, inhibition of D5D diminishes the glutathione peroxidase 4 (GPX4) inhibitor RSL3-induced ferroptosis in YCC-16 gastric cancer cells. However, the addition of AA to D5D depleted gastric cancer cells could reverse the effect of D5D inhibition, restoring the ferroptosis sensitivity of cancer cells (Fig.2). Not only D5D but also elongation of very long-chain fatty acid protein 5 (ELOVL5) is essential for ferroptosis. During n-6 PUFA synthesis, ELOVL5 catalyzes gamma-linolenic acid to DGLA, which is the substrate of D5D. Inhibition of ELOVL5 decreases the sensitivity of cancer cells to ferroptosis [5]. However, the addition of exogenous D5D substrate (DGLA) triggers cell death via activating the ferroptosis pathway in fibrosarcoma cells. Worth noting, this phenomenon has been observed in cells treated with a high dose of DGLA (500 μ M), whereas low dose (less than 250 μ M) appears no anti-cancer effect *in vitro* [77]. Therefore, D5D may serve as a central checkpoint in ferroptosis via manipulating PUFA synthesis [5].

Inhibition of D5D as a new strategy for cancer treatment

Since D5D is an independent prognostic biomarker in many types of cancers, targeting D5D seems like a promising alternative strategy for cancer therapy. By transfecting laryngeal cancer cells with lentivirus vector with *FADS1* shRNA, Zhao et al. have demonstrated that D5D knockdown could inhibit cancer cell proliferation and migration. Additionally, D5D knocking down cells also exhibit the prolonged G1 phase and more apoptosis, indicating that inhibition of D5D expression could suppress laryngeal cancer cell growth. The microarray assay and protein-protein interaction network further indicate that the effect of D5D knocking down may associate with the AKT/mTOR pathway.

Studies have demonstrated that PGE₂ could activate PI3K/AKT/mTOR pathway via acting through EP2/4 receptors, increasing AKT, p670S6K, and S6 phosphorylation in cancer cells [79]. Since silencing D5D decreases PGE₂ production, it has been found that AKT/mTOR pathway is inactivated in tumor tissues after D5D knockdown [14]. Although more studies need to be done to elucidate how PGE₂ connects D5D and AKT/mTOR pathway, it is plausible that the effect of D5D on the AKT/mTOR pathway may depend on PGE₂ production in cancer cells [14].

Not only inhibition of PGE₂ generation, but suppression of D5D may also boost free radical reactions by reprogramming COX-2-catalyzed DGLA peroxidation (Fig. 3). Xiao et al. have identified a series of free radicals from DGLA peroxidation by LC/ESR/MS with α -(4-Pyridyl 1-oxide)-N-tert-butylnitron (POBN), which is a spin trap for stabilizing free radicals. Two unique free radicals (POBN adducts) have been identified from DGLA/COX-2 C-8 oxygenation, POBN/[•]C₇H₁₃O₂ (m/z 324) and POBN/[•]C₈H₁₅O₃ (m/z 354). These two free radicals appear exclusively in DGLA peroxidation, but not AA peroxidation, indicating that alternative downstream pathways of DGLA are existing rather than the AA/PGE₂ pathway [80]. Gu et al. have further improved the spin trapping/solid-phase extraction approach and investigated the association between these two free radicals and colon cancer cell growth. In a cellular environment, [•]C₇H₁₃O₂ and [•]C₈H₁₅O₃ could immediately capture hydrogen to form corresponding derivatives, heptanoic acid, and 8-hydroxyoctanoic acid (8-HOA). MTS assay and cell cycle analysis suggest that 8-HOA could decrease the cell viability and delay the G₁ phase of HCA-7 colon cancer cells. However, heptanoic acid does not affect the cancer cell cycle and proliferation [81]. To better understand the role of DGLA-derived free radicals in cancer, Xu et al. have assessed the apoptosis of HCA-7 colon cancer cells treated with 8-HOA or hexanol. 8-HOA (1 μ M) significantly induces apoptosis in colon cancer cells by regulating the protein expression of p53 and procaspase-9. However, the effect of other DGLA's free radical derivatives (hexanol and heptanoic acid) on apoptosis is modest. Moreover, 8-HOA also drops the IC₅₀ of fluorouracil (5-FU) on HCA-7 cells from 1 mM to 0.5 mM, indicating that 8-HOA may serve as the supplementary treatment for chemotherapy [82]. Moreover, Yang et al. have found that 8-HOA also could suppress the BxPC-3 pancreatic cancer cell proliferation and promote apoptosis. Additionally, the wound healing assay suggests that 8-HOA could inhibit the migration of HCA-7 and BxPC-3 cancer cells. The addition of 8-HOA significantly enhances the efficacy of gemcitabine (first-line chemo) on pancreatic cancer. Interestingly, the increased protein expression of acetyl-histone H3 has been observed in both colon and pancreatic cancer cells treated with 8-HOA, indicating that histone deacetylase (HDAC) may act as the downstream effector of 8-HOA [83]. The HDAC activity response curve to 8-HOA has been established on A549 lung cancer cells [6]. A similar effect of 8-HOA also has been observed in breast cancer cells (MDA-MB 231 and 4T1) [7]. Therefore, it is reasonable to believe that 8-HOA is a broad-spectrum antitumor agent that regulating many aspects of cancer progression.

However, it has been observed in the above-mentioned studies that the treatment of 8-HOA alone without combination with other chemotherapies only can result in less than 30% of inhibition of cancer cell growth. One possible reason is that the effect of exogenous 8-HOA cannot fully represent the effect of endogenous 8-HOA, which is derived from [•]C₈H₁₅O₃ [80]. Although the free radical form of 8-HOA ([•]C₈H₁₅O₃) is transient in the cellular environment, it may still provide additional cytotoxicity rather than the derivate form of 8-HOA (C₈H₁₆O₃). However, in normal cellular conditions, the free radical form of 8-HOA ([•]C₈H₁₅O₃) is not the main product of DGLA, which is more likely to be converted to AA by D5D. To enforce the generation of 8-HOA, Xu et al. have knocked down D5D in HCA-7 cells by siRNA transfection. The DGLA consumption is significantly slower in D5D knockdown cells compared to cells with full D5D expression. After 48 h of the transfection, the 8-HOA level increases from ~0.3 μ M to more than 0.8 μ M, indicating the activation of the DGLA/8-HOA pathway. It

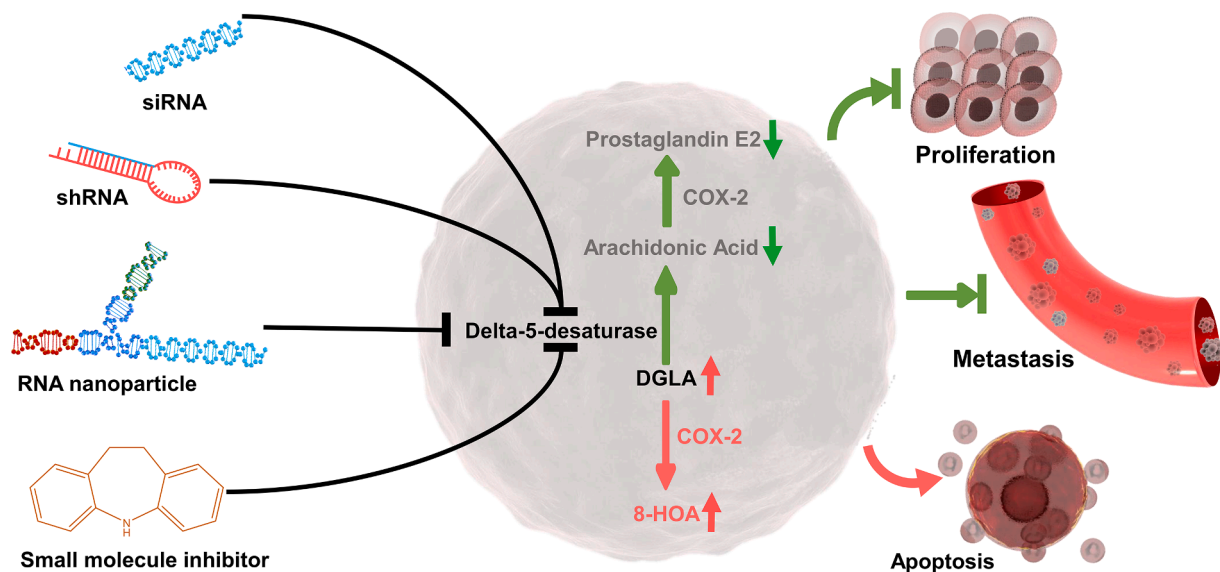


Fig. 3. Inhibition of D5D as a new strategy for cancer treatment. Inhibition of D5D suppresses the AA/PGE₂ generation in cancer cells as shown in green arrows. The alternative pathway could be activated to promote 8-HOA formation from COX-2 catalyzed DGLA peroxidation as shown in red arrows (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

has been observed that supplementation of DGLA (100 μ M) to D5D knockdown cells could activate p53-dependent apoptosis and enhance the effect of 5-FU, irinotecan, and regorafenib [84]. A similar effect of D5D siRNA-based treatment has also been found in pancreatic and breast cancer cells [85,86]. By cross-comparison of all these studies, breast cancer cells (4T1 and MDA-MB 231) generate more 8-HOA (\sim 1.2 μ M) than colon and pancreatic cancer cells (\sim 0.8 μ M). Interestingly, an *in vitro* threshold of endogenous 8-HOA level (0.5 μ M) has been identified in these studies. The effect of D5D knockdown only can be elicited on cancer cells if the threshold (0.5 μ M 8-HOA) is achieved [84–86]. Therefore, the effectiveness of the long-term exposure of just above the threshold concentration 8-HOA may be superior to a high concentration 8-HOA with a short exposure time on cancer cells. This phenomenon may also explain why a high concentration of exogenous 8-HOA appears a lower efficacy with a low concentration of DGLA-derived 8-HOA. The endogenous 8-HOA could be continuously produced from DGLA, resulting in above the threshold concentration of 8-HOA for a long period in cancer cells.

Despite the high efficiency of D5D siRNA, the off-target effect and stability are still the major concerns of RNA-based drugs, especially in animal models and patients [87]. To ensure the continuous generation of 8-HOA, Yang et al. have established the stable D5D knockdown cancer cells using shRNA transfection. Supplementation of DGLA to D5D shRNA transfected BxPC-3 and HCA-7 cancer cells inhibit the protein expression of matrix metalloproteinase 2 and 9 (MMP2/9), which are key enzymes for degradation of type IV collagen, extracellular matrix, and basement membrane [83]. Additionally, knocking down D5D triggers the expression of cell adhesion protein E-cadherin but decreases the expression of structural protein vimentin and snail, which are critical proteins for EMT during cancer metastasis [7]. Not only exogenous 8-HOA, but DGLA-derived endogenous 8-HOA also enhances the inhibitory effect of gemcitabine and 5-FU on pancreatic and colon cancer cells possibly through co-regulating transcriptional activation of genes in cancer metastasis pathways [83]. Furthermore, the *in vivo* study has demonstrated that D5D shRNA transfected tumor tissues only have about a half expression of D5D compared to mice bearing wild-type tumors. Lacking D5D expression limits the AA generation and significantly improves the 8-HOA production from \sim 0.1 to \sim 0.5 μ g/g in tumor tissues. Consequently, about 26% tumor size reduction has been observed in nude mice with D5D shRNA transfection [88].

To further improve the efficiency of the D5D knocking down

approach, Xu et al. have employed the targeted 3-way junction (3WJ) RNA nanoparticle to deliver the D5D siRNA to the tumor region [89]. Unlike other nanoparticles, RNA nanoparticle does not encapsulate the drug/siRNA in the center; however, all the therapeutic siRNA/miRNA are directly conjugated on the branches of the RNA nanoparticle core [90]. The excellent thermodynamical and chemical stability of the 3WJ RNA nanoparticle improves the *in vivo* performance of D5D siRNA. Moreover, tumor-targeting is achieved by adding epithelial cell adhesion molecule (EpCAM) aptamer to one strand of the 3WJ RNA nanoparticle [89]. EpCAM specifically expresses in various types of cancer cells, including colon, lung, and breast cancer cells [91]. Thus, EpCAM aptamer could ensure the binding between nanoparticles and cancer cells. In the xenograft colon cancer model, EpCAM-D5D siRNA nanoparticle significantly increases the 8-HOA production, resulting in about 70% tumor reduction [89]. Shah et al. further expand the benefit of EpCAM-D5D siRNA nanoparticle to breast cancer therapy. Supplementation of DGLA along with EpCAM-D5D siRNA nanoparticle suppresses the tumor growth in orthotopic breast cancer model *via* activating the intrinsic apoptotic pathway. Moreover, they have confirmed that EpCAM-D5D siRNA nanoparticles could inhibit the metastasis of breast cancer cells from the fourth mammary pad to the lung [7]. However, the safety and targeting efficiency of this EpCAM-D5D siRNA nanoparticle on tumor treatment is still unknown. Pang et al. have explored the targeting efficiency and safety of EpCAM-D5D siRNA nanoparticles in lung cancer by comparing the internalization and effect of this nanoparticle on cancer cells versus normal cells. More nanoparticle internalization has been found in A549 lung cancer cells than BEAS-2B normal lung epithelial cells after 4 h of incubation. The selectivity of this nanoparticle is contributed by the EpCAM aptamer that allows nanoparticles to specifically bind to lung cancer cells with high EpCAM expression, whereas it avoids harassing normal cells with low EpCAM expression. Furthermore, it has been observed that the effect of EpCAM-D5D siRNA nanoparticles on A549 cells is better than H1299 lung cancer cells, which have less COX-2 expression. Thus, not only EpCAM but also COX-2 overexpression seems an essential premise for eliciting the effect of EpCAM-D5D siRNA nanoparticles on cancer [6]. Given the fact that COX-2 is the main enzyme for regulating inflammation, more studies need to be conducted to investigate the role of D5D and D5D inhibition-based strategies in the inflammatory tumor microenvironment by involving cytokines and immune cells in consideration. More importantly, since anti-inflammatory agents are widely used in cancer

patients for co-treatment of cancer-associated symptoms, patients may gain extra benefit from the possible synergy effect between D5D inhibition-based strategy and anti-inflammatory treatments.

Previous studies have demonstrated that D5D could regulate many aspects of cancer progression, including survival, proliferation, migration, invasion, apoptosis, and cell cycle arrest [6,7,84–86]. It raises the question of how this D5D inhibition-based strategy results in such diverse effects on cancer. One possible explanation is that D5D inhibition could break the bridge between the PGE₂ and PI3K/Akt/mTOR pathway, which is participated in almost all the aspects of cancer progression [14]. For instance, the PI3K/Akt pathway can activate mTOR, resulting in cancer cell growth and proliferation; Akt regulates BAX/Bcl-2 balance, caspase cleavage, and PARP activation, suppressing apoptosis [92]. Furthermore, given that ULK, FIP200, and ATG13 can be suppressed by mTOR, inhibition of D5D may trigger autophagy in cancer cells [93]. The diverse anti-cancer properties of D5D inhibition may also be attributed to the DGLA-derived 8-HOA, which shared a similar structure with the classical HDAC inhibitor valproic acid. The previous studies have indicated that the overall activity of HDAC in cancer cells can be inhibited by 8-HOA without influencing histone acetyltransferase (HAT) activity. Additionally, the activity of sirtuins (class III HDACs, NAD⁺ dependent) is consistent in cancer cells before and after D5D siRNA transfection. Therefore, 8-HOA may inhibit cancer cell growth via inhibiting HDAC I, II, and/or IV (Zinc dependent) [6]. Moreover, 8-HOA also could regulate YAP1/TAZ pathway and downstream molecules in cancer cells. Indeed, it has been observed in lung cancer cells that supplementation of DGLA and treatment of EpCAM-D5D siRNA nanoparticle suppresses the protein expression and nuclear translocation of YAP1 and TAZ [6]. As the downstream effector of the Hippo pathway, YAP1/TAZ can be activated when Hippo is off, resulting in the promotion of cancer cell growth and proliferation. Interestingly, this phenomenon has not been observed in cancer cells treated with DGLA or EpCAM-D5D siRNA nanoparticles alone, implicating the crucial role of DGLA-derived 8-HOA in YAP1/TAZ signaling [6]. Not only genetically knocking down, but small molecule D5D inhibitor may also hold promise for cancer treatment. However, classical D5D inhibitors, such as sesamin, curcumin, and CP-24879 could not specifically block the activity of D5D [94–96]. Thus, even though these inhibitors display an ideal inhibitory effect on cancer, it is unconvincing that the effect of these inhibitors is exclusively coming from D5D inhibition. For instance, CP-24879 is a mixed D5D and D6D inhibitor. The ABMC-7 cell-based desaturase assay suggests that CP-24879 could decrease the generation of leukotriene C4 and AA via nonspecifically inhibiting D5D and D6D activity [96]. However, the inhibition of D6D may raise safety concerns, since inadequate D6D is correlating with chronic inflammatory diseases, such as diabetic neuropathy and atopic eczema [97,98]. In contrast, sesamin and curcumin have better specificity on D5D. In liver microsome assay, curcumin could inhibit 49% of D5D and 18% D6D, whereas sesamin barely inhibits D6D, D9D, and D12D [99,100]. The anti-cancer properties of sesamin and curcumin have been widely studied in different types of cancers [101,102]. Notably, curcumin has been involved in several clinical trials (stage I to III) for the treatment of breast, prostate, and cervical and uterine cancers [101]. Although many studies have demonstrated the effect of sesamin and curcumin on cancer *in vivo* and *in vitro* [103–107]. We are still unclear what is the role of D5D in the anti-cancer properties of sesamin and curcumin. Given that inflammatory cytokines, such as TNF- α and NF- κ B, are important downstream targets of sesamin and curcumin [108,109], these natural inhibitors may affect inflammatory tumor microenvironment (TME) via regulating D5D activity. Furthermore, several selective D5D inhibitors have been identified by Takeda Pharmaceutical Company, such as D5D-IN-326, T-3364366, and 3,5-diphenyl-4-methyl-1,3-oxazolidin-2-ones; however, the effect and mechanism of these molecules have only been evaluated in metabolic diseases (such as insulin resistance, obesity, and atherosclerosis) rather than cancer [110–113]. Additionally, another molecule iminodibenzyl has recently been found as a

promising D5D inhibitor. Iminodibenzyl could redirect COX-2 catalyzed DGLA peroxidation, resulting in the generation of 8-HOA in cancer cells [114,115]. The slow advance of the development of D5D inhibitors may be reasoned by (1) the missing identification of the fine crystal structure of the D5D enzyme and (2) the difficulty to obtain D5D with high stability and activity [10]. Another obstacle is the current methods to quantify PUFAs metabolites of D5D are laborious and time-consuming. Thus, a faster and reliable method needs to be established for accelerating the development of D5D inhibitors for cancer treatment. The high sensitive electrochemical sensor may be the answer. For instance, a recent study has demonstrated that a 2D nanomaterial Ti3C2 MXene-based sensor could simplify the procedures for assessing PGE₂ and 8-HOA concentration in cell lysis, tumor tissues, and blood [116].

Discussion and conclusion

PUFAs are essential nutrition in our daily diet [117]. Unbalanced PUFAs uptake is associated with various diseases statuses, including inflammation, cardiovascular diseases, type 2 diabetes, and cancer [9, 32,45]. According to the traditional concept, the n-3 PUFAs are anti-inflammatory, whereas n-6 PUFAs are pro-inflammatory [118]. Indeed, AA could be produced in the n-6 PUFAs pathway, resulting in the production of PGs by COX-2 [117,118]. PGs, especially PGE₂, play a critical role in immune diseases and inflammation through regulating mast cell activation, T_H1 cell differentiation, T_H17 cell proliferation, and cytokine production [119–121]. Give that inflammation is a key factor in cancer progression, previous studies have investigated the role of the n-6 PUFAs pathway in cancers [77,122–125]. The COX-2/PGE₂ axis could directly activate EP receptors on cancer cells, resulting in cancer cell proliferation, invasion, EMT, and angiogenesis [52,54,79,126,127]. Additionally, PGE₂ from cancer cells also could affect EP receptors on endothelial cells in a paracrine pattern [128–131]. Moreover, EP receptors are presenting in immune cells, such as MDSCs, macrophage, NK cells, dendritic cells, and T lymphocytes [53,132–137]. The cancer cell or immune cell-derived PGE₂ could bind to these EP receptors, creating an immune suppressor TME [47]. Therefore, suppression of PGE₂ production in cancer cells by using COX-2 inhibitors may be a promising anti-cancer strategy.

However, clinical trials suggest that COX-2 inhibitors fail to improve the overall survival and progression-free survival of cancer patients [67, 138]. Even worse, the long-term and high-dose COX-2 inhibitors for cancer patients may cause severe side effects, such as myocardial infarction [64,66,139]. Therefore, it is essential to develop a better strategy for cancer therapy by regulating the AA/PGE₂ axis. Recent studies have revealed that D5D could be a desirable target for cancer treatment [14,81,82]. D5D is the rate-limiting enzyme catalyzing the formation of AA from DGLA [9]. Inhibition of D5D, either protein expression or activity, suppresses the production of AA and PGE₂ [84–86]. Interestingly, in the cellular condition of D5D inhibition, DGLA could be converted to a distinct free radical byproduct, 8-HOA by COX-2 in cancer cells. 8-HOA inhibits cancer cell proliferation, migration, invasion, and promotes apoptosis via decreasing HDAC activity and YAP1/TAZ pathway in cancer cells. Consequently, cancer growth could be inhibited by the decrease of PGE₂ and the increase of 8-HOA levels [82,84–86,88,89]. The benefit of RNAi-based genetical knockdown of D5D, such as siRNA, shRNA, and RNA nanoparticles, have been confirmed in colon, pancreatic, breast, and lung cancers *in vitro* and *in vivo* [6,7,83–86,89]. Additionally, small molecule D5D inhibitors also have been identified in cell-based or rat liver microsomes assays, including sesamin, curcumin, D5D-IN-326, CP-24879, iminodibenzyl, etc [94,95,110,112,115,140]. Although iminodibenzyl efficiently suppresses lung cancer cell growth and metastasis [115], more studies need to be done to further explore the effect and mechanisms of other D5D small molecule inhibitors in cancer. Moreover, D5D may have different roles in cancer by simultaneously regulating multiple pathways. For example, a recent study indicates that D5D expression is differential in

mesenchymal-type and intestinal-type gastric cancer cells. D5D may serve as an essential enzyme in cancer cell ferroptosis [5]. Therefore, it is plausible that inhibition of D5D may activate apoptosis but suppress ferroptosis in cancer cells. Elucidating why D5D has the opposite effect on apoptosis versus ferroptosis in cancer cells may help us to develop a better anti-cancer strategy in the future.

In conclusion, D5D is the key enzyme for regulating PUFA synthesis. The D5D and certain SNPs expressions are associated with cancer progression. In the n-6 PUFA synthesis pathway, DGLA is catalyzed by D5D to form AA, which is a precursor of PGE₂, an inflammation mediator. The COX-2 catalyzed PGE₂ could activate EP receptors and promote cancer cell growth and metastasis via regulating tumor microenvironment and immunosuppression. While the opposite function of D5D has been revealed in recent studies that D5D could trigger ferroptosis response in cancer cells via manipulating PUFA synthesis, leading to programmed cancer cell death. Additionally, in case of the absence of D5D, the downstream enzyme COX-2 also could directly catalyze DGLA peroxidation, resulting in the generation of a distinct anti-cancer free radical byproduct, 8-HOA in cancer cells. It has been demonstrated that inhibition of D5D could activate the apoptosis pathway but suppress cancer cell survival, proliferation, migration, and invasion. All these reports have suggested that D5D may serve as the central hub and ideal target for regulating different aspects of cancer progression. Despite the high efficiency of RNA nanoparticle-based siRNA treatment, continued research into selective D5D inhibitors may help elucidate the controversial mechanisms underlying PUFAs metabolism in cancer and may aid the development of novel therapeutical strategies.

CRedit authorship contribution statement

Lizhi Pang: Conceptualization, Visualization, Writing – original draft. **Harshit Shah:** Writing – review & editing. **Yi Xu:** Writing – review & editing. **Steven Qian:** Conceptualization, Supervision, Writing – original draft.

Declaration of Competing Interest

Steven Qian is an inventor on a patent (US-2019070193-A1) related to this work filed by NDSU Research Foundation. The authors declare no other competing interests.

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References

- [1] M.T. Nakamura, T.Y. Nara, Structure, function, and dietary regulation of $\delta 6$, $\delta 5$, and $\delta 9$ desaturases, *Annu. Rev. Nutr.* 24 (2004) 345–376, <https://doi.org/10.1146/annurev.nutr.24.121803.063211>.
- [2] M. Matsuda, T. Kawamoto, R. Tamura, Predictive value of serum dihomo- γ -linolenic acid level and estimated Δ -5 desaturase activity in patients with hepatic steatosis, *Obes. Res. Clin. Pract.* 11 (2017) 34–43, <https://doi.org/10.1016/j.orcp.2016.02.004>.
- [3] V. Lamantia, S. Bissonnette, V. Provost, M. Devaux, Y. Cyr, C. Daneault, C. D. Rosiers, M. Faraj, The association of polyunsaturated fatty acid δ -5-desaturase activity with risk factors for type 2 diabetes is dependent on plasma ApoB-lipoproteins in overweight and obese adults, *J. Nutr.* 149 (2019) 57–67, <https://doi.org/10.1093/jn/nxy238>.
- [4] M.A. Lankinen, A. Fauland, B.I. Shimizu, J. Ågren, C.E. Wheelock, M. Laakso, U. Schwab, J. Pihlajamäki, Inflammatory response to dietary linoleic acid depends on FADS1 genotype, *Am. J. Clin. Nutr.* 109 (2019) 165–175, <https://doi.org/10.1093/ajcn/nqy287>.
- [5] J.Y. Lee, M. Nam, H.Y. Son, K. Hyun, S.Y. Jang, J.W. Kim, M.W. Kim, Y. Jung, E. Jang, S.J. Yoon, J. Kim, J. Kim, J. Seo, J.K. Min, K.J. Oh, B.S. Han, W.K. Kim, K. H. Bae, J. Song, J. Kim, Y.M. Huh, G.S. Hwang, E.W. Lee, S.C. Lee, Polyunsaturated fatty acid biosynthesis pathway determines ferroptosis sensitivity in gastric cancer, *Proc. Natl Acad. Sci.* 117 (2020) 32433–32442, <https://doi.org/10.1073/pnas.2006828117>.
- [6] L. Pang, H. Shah, H. Wang, D. Shu, S.Y. Qian, V. Sathish, EpCAM-targeted 3WJ RNA nanoparticle harboring delta-5-desaturase siRNA inhibited lung tumor formation via DGLA peroxidation, *Mol. Ther. Nucleic Acids* 22 (2020) 222–235, <https://doi.org/10.1016/j.omtn.2020.08.024>.
- [7] H. Shah, L. Pang, H. Wang, D. Shu, S.Y. Qian, V. Sathish, Growth inhibitory and anti-metastatic activity of epithelial cell adhesion molecule targeted three-way junctional delta-5-desaturase siRNA nanoparticle for breast cancer therapy, *Nanomed. Nanotechnol. Biol. Med.* 30 (2020), 102298, <https://doi.org/10.1016/j.nano.2020.102298>.
- [8] F. Tosi, F. Sartori, P. Guarini, O. Olivieri, N. Martinelli, Delta-5 and delta-6 desaturases: crucial enzymes in polyunsaturated fatty acid-related pathways with pleiotropic influences in health and disease, *Adv. Exp. Med. Biol.* 824 (2014) 61–81, <https://doi.org/10.1007/978-3-319-07320-0-7>.
- [9] J.M. Lee, H. Lee, S. Kang, W.J. Park, Fatty Acid Desaturases, polyunsaturated fatty acid regulation, and biotechnological advances, *Nutrients* 8 (2016), <https://doi.org/10.3390/nu8010023>.
- [10] M.C. Mansilla, C.E. Banchio, D. de Mendoza, Signalling pathways controlling fatty acid desaturation, *Subcell. Biochem.* 49 (2008) 71–99, <https://doi.org/10.1007/978-1-4020-8831-5-3>.
- [11] M. Wolters, C. Dering, A. Siani, P. Russo, J. Kaprio, P. Risé, L.A. Moreno, S. De Henauw, K. Mehlig, T. Veidebaum, D. Molnár, M. Tornaritis, L. Iacoviello, Y. Pitsiladis, C. Galli, R. Foraita, C. Böhrhorst, The role of a FADS1 polymorphism in the association of fatty acid blood levels, BMI and blood pressure in young children—analyses based on path models, *PLoS One* 12 (2017), <https://doi.org/10.1371/journal.pone.0181485>.
- [12] V. Nobili, A. Alisi, Z. Liu, T. Liang, A. Crudele, M. Raponi, J. Lin, N.P. Chalasani, W. Liu, In a pilot study, reduced fatty acid desaturase 1 function was associated with nonalcoholic fatty liver disease and response to treatment in children, *Pediatr. Res.* 84 (2018) 696–703, <https://doi.org/10.1038/s41390-018-0132-7>.
- [13] F. Jiao, H. Sun, Q. Yang, H. Sun, Z. Wang, M. Liu, J. Chen, Identification of FADS1 through common gene expression profiles for predicting survival in patients with bladder cancer, *Cancer Manag. Res.* 12 (2020) 8325–8339, <https://doi.org/10.2147/CMAR.S254316>.
- [14] R. Zhao, L. Tian, B. Zhao, Y. Sun, J. Cao, K. Chen, F. Li, M. Li, D. Shang, M. Liu, FADS1 promotes the progression of laryngeal squamous cell carcinoma through activating AKT/mTOR signaling, *Cell Death. Dis.* 11 (2020) 1–14, <https://doi.org/10.1038/s41419-020-2457-5>.
- [15] D.A. Los, N. Murata, Structure and expression of fatty acid desaturases, *Biochim. Biophys Acta BBA Lipids Lipid Metab.* 1394 (1998) 3–15, [https://doi.org/10.1016/S0005-2760\(98\)0091-5](https://doi.org/10.1016/S0005-2760(98)0091-5).
- [16] P.C. Calder, 1 - Nutritional benefits of omega-3 fatty acids, in: C. Jacobsen, N. S. Nielsen, A.F. Horn, A.D.M. Sørensen (Eds.), *Food Enrichment with Omega-3 Fatty Acids*, Woodhead Publishing, 2013, pp. 3–26, <https://doi.org/10.1533/9780857098863.1.3>.
- [17] X. Wang, H. Lin, Y. Gu, Multiple roles of dihomo- γ -linolenic acid against proliferation diseases, *Lipids Health Dis.* 11 (2012) 25, <https://doi.org/10.1186/1476-511X-11-25>.
- [18] S. Athinarayanan, Y.Y. Fan, X. Wang, E. Callaway, D. Cai, N. Chalasani, R. S. Chapkin, W. Liu, Fatty acid desaturase 1 influences hepatic lipid homeostasis by modulating the PPAR α -FGF21 axis, *Hepatol. Commun.* 5 (2021) 461–477, <https://doi.org/10.1002/hep4.1629>.
- [19] A.D. Gromovsky, R.C. Schugar, A.L. Brown, R.N. Helsley, A.C. Burrows, D. Ferguson, R. Zhang, B.E. Sansbury, R.G. Lee, R.E. Morton, D.S. Allende, J. S. Parks, M. Spite, J.M. Brown, The Δ -5 fatty acid desaturase FADS1 impacts metabolic disease by balancing pro-inflammatory and pro-resolving lipid mediators, *Arterioscler. Thromb. Vasc. Biol.* 38 (2018) 218–231, <https://doi.org/10.1161/ATVBAHA.117.309660>.
- [20] R. Daneshmand, S. Kurl, T.P. Tuomainen, J.K. Virtanen, Associations of estimated Δ -5-desaturase and Δ -6-desaturase activities with stroke risk factors and risk of stroke: the kuopio ischaemic heart disease risk factor study, *Br. J. Nutr.* 117 (2017) 582–590, <https://doi.org/10.1017/S000711451700054X>.
- [21] I. Swenne, B. Vessby, Relationship of Δ (6)-desaturase and Δ (5)-desaturase activities with thyroid hormone status in adolescents with eating disorders and weight loss, *Acta Paediatr.* 102 (2013) 416–418, <https://doi.org/10.1111/apa.12132>.
- [22] M. Xiang, M.A. Rahman, H. Ai, X. Li, L.S. Harbige, Diet and gene expression: delta-5 and delta-6 desaturases in healthy chinese and European subjects, *Ann. Nutr. Metab.* 50 (2007) 492–498.
- [23] T. Matsuzaka, H. Shimano, N. Yahagi, M. Amemiya-Kudo, T. Yoshikawa, A. H. Hasty, Y. Tamura, J. Osuga, H. Okazaki, Y. Iizuka, A. Takahashi, H. Sone, T. Gotoda, S. Ishibashi, N. Yamada, Dual regulation of mouse Delta(5)- and Delta (6)-desaturase gene expression by SREBP-1 and PPARalpha, *J. Lipid Res.* 43 (2002) 107–114.
- [24] H.S. Dashti, I. Daghlas, J.M. Lane, Y. Huang, M.S. Udler, H. Wang, H.M. Ollila, S. E. Jones, J. Kim, A.R. Wood, M.N. Weedon, S. Aslibekyan, M. Garaulet, R. Saxena, Genetic determinants of daytime napping and effects on cardiometabolic health, *Nat. Commun.* 12 (2021) 900, <https://doi.org/10.1038/s41467-020-20585-3>.
- [25] R. Valenzuela, M.A. Rincón-Cervera, F. Echeverría, C. Barrera, A. Espinosa, M. C. Hernández-Rodas, M. Ortiz, A. Valenzuela, L.A. Videla, Iron-induced pro-oxidant and pro-lipogenic responses in relation to impaired synthesis and accretion of long-chain polyunsaturated fatty acids in rat hepatic and extrahepatic tissues, *Nutrition* 45 (2018) 49–58, <https://doi.org/10.1016/j.nut.2017.07.007>.
- [26] Y. Lu, J. Shao, X. Shu, Y. Jiang, J. Rong, Y. Lai, J. Liu, FADS1 is a prognostic biomarker in bladder cancer: a study based on TCGA data, *Comb. Chem. High*

- Throughput Screen. (2020), <https://doi.org/10.2174/1386207323666200925104911>.
- [27] D. Wang, Y. Lin, B. Gao, S. Yan, H. Wu, Y. Li, Q. Wu, Y. Wei, Reduced expression of FADS1 predicts worse prognosis in non-small-cell lung cancer, *J. Cancer* 7 (2016) 1226–1232, <https://doi.org/10.7150/jca.15403>.
- [28] Y. Du, S.M. Yan, W.Y. Gu, F. He, L.Y. Huang, M. Li, Y. Yuan, R.H. Chen, Q. Zhong, M.Z. Li, Y. Li, M.S. Zeng, Decreased expression of FADS1 predicts a poor prognosis in patients with esophageal squamous cell carcinoma, *Asian Pac. J. Cancer Prev.* 16 (2015) 5089–5094, <https://doi.org/10.7314/apjcp.2015.16.12.5089>.
- [29] H. Lian, P. Xie, N. Yin, J. Zhang, X. Zhang, J. Li, C. Zhang, Linc00460 promotes osteosarcoma progression via miR-1224-5p/FADS1 axis, *Life Sci.* 233 (2019), 116757, <https://doi.org/10.1016/j.lfs.2019.116757>.
- [30] B. Zhang, W.H. Jia, K. Matsuda, S.S. Kweon, K. Matsuo, Y.B. Xiang, A. Shin, S. H. Jee, D.H. Kim, Q. Cai, J. Long, J. Shi, W. Wen, G. Yang, Y. Zhang, C. Li, B. Li, Y. Guo, Z. Ren, B.T. Ji, Z.Z. Pan, A. Takahashi, M.H. Shin, F. Matsuda, Y.T. Gao, J. H. Oh, S. Kim, Y.O. Ahn, A.T. Chan, J. Chang-Claude, M.L. Slattery, S.B. Gruber, F.R. Schumacher, S.L. Stenzel, G. Casey, H.R. Kim, J.Y. Jeong, J.W. Park, H.L. Li, S. Hosono, S.H. Cho, M. Kubo, X.O. Shu, Y.X. Zeng, W. Zheng, Large-scale genetic study in East Asians identifies six new loci associated with colorectal cancer risk, *Nat. Genet.* 46 (2014) 533–542, <https://doi.org/10.1038/ng.2985>.
- [31] X.Y. Qin, T. Su, W. Yu, S. Kojima, Lipid desaturation-associated endoplasmic reticulum stress regulates MYCN gene expression in hepatocellular carcinoma cells, *Cell Death. Dis.* 11 (2020) 1–13, <https://doi.org/10.1038/s41419-020-2257-y>.
- [32] R. Wall, R.P. Ross, G.F. Fitzgerald, C. Stanton, Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids, *Nutr. Rev.* 68 (2010) 280–289, <https://doi.org/10.1111/j.1753-4887.2010.00287.x>.
- [33] F. Chen, B. He, L. Yan, Y. Qiu, L. Lin, L. Cai, FADS1 rs174549 polymorphism may predict a favorable response to chemoradiotherapy in oral cancer patients, *J. Oral Maxillofac. Surg.* 75 (2017) 214–220, <https://doi.org/10.1016/j.joms.2016.07.005>.
- [34] C. Wang, N. Qin, M. Zhu, M. Chen, K. Xie, Y. Cheng, J. Dai, J. Liu, Y. Xia, H. Ma, G. Jin, C.I. Amos, Z. Hu, D. Lin, H. Shen, Metabolome-wide association study identified the association between a circulating polyunsaturated fatty acids variant rs174548 and lung cancer, *Carcinogenesis* 38 (2017) 1147–1154, <https://doi.org/10.1093/carcin/bgx084>.
- [35] N. Song, A. Shin, J.W. Park, J. Kim, J.H. Oh, Common risk variants for colorectal cancer: an evaluation of associations with age at cancer onset, *Sci. Rep.* 7 (2017), <https://doi.org/10.1038/srep40644>.
- [36] Q. Wei, D. Yu, M. Liu, M. Wang, M. Zhao, M. Liu, W. Jia, H. Ma, J. Fang, W. Xu, K. Chen, Z. Xu, J. Wang, L. Tian, H. Yuan, J. Chang, Z. Hu, L. Wei, Y. Huang, Y. Han, J. Liu, D. Han, H. Shen, S. Yang, H. Zheng, Q. Ji, D. Li, W. Tan, C. Wu, D. Lin, Genome-wide association study identifies three susceptibility loci for laryngeal squamous cell carcinoma in the Chinese population, *Nat. Genet.* 46 (2014) 1110–1114, <https://doi.org/10.1038/ng.3090>.
- [37] F. Chen, T. Lin, L. Yan, F. Liu, J. Huang, F. Liu, J. Wu, Y. Qiu, L. Lin, L. Cai, B. He, Novel polymorphism in FADS1 gene and fish consumption on risk of oral cancer: a case-control study in southeast China, *Oncotarget* 8 (2017) 15887–15893, <https://doi.org/10.18632/oncotarget.15069>.
- [38] S. Saito, H. Ozawa, Y. Imanishi, M. Sekimizu, Y. Watanabe, F. Ito, Y. Ikari, N. Nakahara, K. Kameyama, K. Ogawa, Cyclooxygenase-2 expression is associated with chemoresistance through cancer stemness property in hypopharyngeal carcinoma, *Oncol. Lett.* 22 (2021) 533, <https://doi.org/10.3892/ol.2021.12794>.
- [39] Y.C. Zhang, H. Zhao, C. Chen, M.A. Ali, COX-2 gene rs689466 polymorphism is associated with increased risk of colorectal cancer among Caucasians: a meta-analysis, *World J. Surg. Oncol.* 18 (2020) 192, <https://doi.org/10.1186/s12957-020-01957-x>.
- [40] S. Wang, H. Gao, J. Zuo, Z. Gao, Cyclooxygenase-2 expression correlates with development, progression, metastasis, and prognosis of osteosarcoma: a meta-analysis and trial sequential analysis, *FEBS Open Bio* 9 (2019) 226–240, <https://doi.org/10.1002/2211-5463.12560>.
- [41] C. Denkert, K.J. Winzer, B.M. Müller, W. Weichert, S. Pest, M. Köbel, G. Kristiansen, A. Reles, A. Siegert, H. Guski, S. Hauptmann, Elevated expression of cyclooxygenase-2 is a negative prognostic factor for disease free survival and overall survival in patients with breast carcinoma, *Cancer* 97 (2003) 2978–2987, <https://doi.org/10.1002/cncr.11437>.
- [42] B. Yang, L. Jia, Q. Guo, H. Ren, Y. Hu, T. Xie, Clinicopathological and prognostic significance of cyclooxygenase-2 expression in head and neck cancer: a meta-analysis, *Oncotarget* 7 (2016) 47265–47277, <https://doi.org/10.18632/oncotarget.10059>.
- [43] S. May-Wilson, A. Sud, P.J. Law, K. Palin, S. Tuupanen, A. Gylfe, U.A. Hänninen, T. Cajuso, T. Tanskanen, J. Kondelin, E. Kaasinen, A.P. Sarin, J.G. Eriksson, H. Rissanen, P. Knekt, E. Pukkala, P. Jousilahti, V. Salomaa, S. Ripatti, A. Palotie, L. Renkonen-Sinisalo, A. Lepistö, J. Böhm, J.P. Mecklin, N.A. Al-Tassan, C. Palleas, S.M. Farrington, M.N. Timofeeva, B.F. Meyer, S.M. Wakil, H. Campbell, C. G. Smith, S. Idziaszczyk, T.S. Maughan, D. Fisher, R. Kerr, D. Kerr, M. N. Passarelli, J.C. Figueiredo, D.D. Buchanan, A.K. Win, J.L. Hopper, M. A. Jenkins, N.M. Lindor, P.A. Newcomb, S. Gallinger, D. Conti, F. Schumacher, G. Casey, L.A. Aaltonen, J.P. Cheadle, I.P. Tomlinson, M.G. Dunlop, R. S. Houlston, Pro-inflammatory fatty acid profile and colorectal cancer risk: a Mendelian randomisation analysis, *Eur. J. Cancer* 84 (2017) 228–238, <https://doi.org/10.1016/j.ejca.2017.07.034>.
- [44] L.M. Dong, X.O. Shu, Y.T. Gao, G. Milne, B.T. Ji, G. Yang, H.L. Li, N. Rothman, W. Zheng, W.H. Chow, C.C. Abnet, Urinary prostaglandin E2 metabolite and gastric cancer risk in the Shanghai women's health study, *Cancer Epidemiol. Biomark. Prev.* 18 (2009) 3075–3078, <https://doi.org/10.1158/1055-9965.EPI-09-0680>.
- [45] N. Koundouros, G. Pouligiannis, Reprogramming of fatty acid metabolism in cancer, *Br. J. Cancer* 122 (2020) 4–22, <https://doi.org/10.1038/s41416-019-0650-z>.
- [46] F. Finetti, C. Travelli, J. Ercoli, G. Colombo, E. Buoso, L. Trabalzini, Prostaglandin E2 and cancer: insight into tumor progression and immunity, *Biology* 9 (2020), <https://doi.org/10.3390/biology9120434> (Basel).
- [47] R. Mizuno, K. Kawada, Y. Sakai, Prostaglandin E2/EP signaling in the tumor microenvironment of colorectal cancer, *Int. J. Mol. Sci.* 20 (2019), <https://doi.org/10.3390/ijms20246254>.
- [48] J. Yin, S.S. Kim, E. Choi, Y.T. Oh, W. Lin, T.H. Kim, J.K. Sa, J.H. Hong, S.H. Park, H.J. Kwon, X. Jin, Y. You, J.H. Kim, H. Kim, J. Son, J. Lee, D.H. Nam, K.S. Choi, B. Shi, H.S. Gwak, H. Yoo, A. Iavarone, J.H. Kim, J.B. Park, ARS2/MAGL signaling in glioblastoma stem cells promotes self-renewal and M2-like polarization of tumor-associated macrophages, *Nat. Commun.* 11 (2020) 2978, <https://doi.org/10.1038/s41467-020-16789-2>.
- [49] A. Kock, K. Larsson, F. Bergqvist, N. Eissler, L.H.M. Elfman, J. Raouf, M. Korotkova, J.I. Johnsen, P.J. Jakobsson, P. Kogner, Inhibition of microsomal prostaglandin E synthase-1 in cancer-associated fibroblasts suppresses neuroblastoma tumor growth, *EBioMedicine* 32 (2018) 84–92, <https://doi.org/10.1016/j.ebiom.2018.05.008>.
- [50] Y. Rong, L. Huang, K. Yi, H. Chen, S. Liu, W. Zhang, C. Yuan, X. Song, F. Wang, Co-administration of sulforaphane and doxorubicin attenuates breast cancer growth by preventing the accumulation of myeloid-derived suppressor cells, *Cancer Lett.* 493 (2020) 189–196, <https://doi.org/10.1016/j.canlet.2020.08.041>.
- [51] N. Komura, S. Mabuchi, K. Shimura, E. Yokoi, K. Kozasa, H. Kuroda, R. Takahashi, T. Sasano, M. Kawano, W. Matsumoto, M. Kodama, K. Hashimoto, K. Sawada, T. Kimura, The role of myeloid-derived suppressor cells in increasing cancer stem-like cells and promoting PD-L1 expression in epithelial ovarian cancer, *Cancer Immunol. Immunother.* 69 (2020) 2477–2499, <https://doi.org/10.1007/s00262-020-02628-2>.
- [52] G. Yan, H. Zhao, Q. Zhang, Y. Zhou, L. Wu, J. Lei, X. Wang, J. Zhang, X. Zhang, L. Zheng, G. Du, W. Xiao, B. Tang, H. Miao, Y. Li, A RIPK3-PGE2 circuit mediates myeloid-derived suppressor cell-potentialized colorectal carcinogenesis, *Cancer Res.* 78 (2018) 5586–5599, <https://doi.org/10.1158/0008-5472.CAN-17-3962>.
- [53] V. Prima, L.N. Kaliberova, S. Kaliberov, D.T. Curriel, S. Kusmartsev, COX2/mPGES1/PGE2 pathway regulates PD-L1 expression in tumor-associated macrophages and myeloid-derived suppressor cells, *Proc. Natl Acad. Sci.* 114 (2017) 1117–1122, <https://doi.org/10.1073/pnas.1612920114>.
- [54] X. Zhang, K. Yan, L. Deng, J. Liang, H. Liang, D. Feng, B. Ling, Cyclooxygenase 2 promotes proliferation and invasion in ovarian cancer cells via the PGE2/NF-κB pathway, *Cell Transplant.* 28 (2019) 1S–13S, <https://doi.org/10.1177/0963689719890597>.
- [55] J.Y. So, N. Skrypeck, H.H. Yang, A.S. Merchant, G.W. Nelson, W.D. Chen, H. Ishii, J.M. Chen, G. Hu, B.R. Achyut, E.C. Yoon, L. Han, C. Huang, M.C. Cam, K. Zhao, M.P. Lee, L. Yang, Induction of DNMT3B by PGE2 and IL6 at distant metastatic sites promotes epigenetic modification and breast cancer colonization, *Cancer Res.* 80 (2020) 2612–2627, <https://doi.org/10.1158/0008-5472.CAN-19-3339>.
- [56] R. Salcedo, X. Zhang, H.A. Young, N. Michael, K. Wasserman, W.H. Ma, M. Martins-Green, W.J. Murphy, J.J. Oppenheim, Angiogenic effects of prostaglandin E2 are mediated by up-regulation of CXCR4 on human microvascular endothelial cells, *Blood* 102 (2003) 1966–1977, <https://doi.org/10.1182/blood-2002-11-3400>.
- [57] F. Finetti, R. Solito, L. Morbidelli, A. Giachetti, M. Ziche, S. Donnini, Prostaglandin E2 regulates angiogenesis via activation of fibroblast growth factor receptor-1, *J. Biol. Chem.* 283 (2008) 2139–2146, <https://doi.org/10.1074/jbc.M703090200>.
- [58] K. Osawa, M. Umemura, R. Nakakaji, R. Tanaka, R.M. Islam, A. Nagasako, T. Fujita, U. Yokoyama, T. Koizumi, K. Mitsudo, Y. Ishikawa, Prostaglandin E2 receptor EP4 regulates cell migration through Orai1, *Cancer Sci.* 111 (2020) 160–174, <https://doi.org/10.1111/cas.14247>.
- [59] H.B. Kim, M. Kim, Y.S. Park, I. Park, T. Kim, S.Y. Yang, C.J. Cho, D. Hwang, J. H. Jung, S.D. Markowitz, S.W. Hwang, S.K. Yang, D.S. Lim, S.J. Myung, Prostaglandin E2 activates YAP and a positive-signaling loop to promote colon regeneration following colitis but also carcinogenesis in mice, *Gastroenterology* 152 (2017) 616–630, <https://doi.org/10.1053/j.gastro.2016.11.005>.
- [60] B. Cen, J.D. Lang, Y. Du, J. Wei, Y. Xiong, N. Bradley, D. Wang, R.N. DuBois, Prostaglandin E2 induces MIR675-5p to promote colorectal tumor metastasis via modulation of p53 expression, *Gastroenterology* 158 (2020) 971–984, <https://doi.org/10.1053/j.gastro.2019.11.013>, e10.
- [61] L. Lin, D. Wang, S. Qu, H. Zhao, Y. Lin, miR-370-3p alleviates ulcerative colitis-related colorectal cancer in mice through inhibiting the inflammatory response and epithelial-mesenchymal transition, *Drug Des. Dev. Ther.* 14 (2020) 1127–1141, <https://doi.org/10.2147/DDDT.S238124>.
- [62] Y.R. Park, S.Y. Seo, S.L. Kim, S.M. Zhu, S. Chun, J.M. Oh, M.R. Lee, S.H. Kim, I. H. Kim, S.O. Lee, S.T. Lee, S.W. Kim, miRNA-206 suppresses PGE2-induced colorectal cancer cell proliferation, migration, and invasion by targeting TM4SF1, *Biosci. Rep.* 38 (2018), <https://doi.org/10.1042/BSR20180664>.
- [63] K. Iwamoto, H. Takahashi, D. Okuzaki, H. Osawa, T. Ogino, N. Miyoshi, M. Umemura, C. Matsuda, H. Yamamoto, T. Mizushima, M. Mori, Y. Doki, H. Eguchi, Syntenin-1 promotes colorectal cancer stem cell expansion and chemoresistance by regulating prostaglandin E2 receptor, *Br. J. Cancer* 123 (2020) 955–964, <https://doi.org/10.1038/s41416-020-0965-9>.
- [64] L.G. Howes, Selective COX-2 inhibitors, NSAIDs and cardiovascular events – is celecoxib the safest choice? *Ther. Clin. Risk Manag.* 3 (2007) 831–845.

- [65] N.K. Altorki, R.S. Keresztes, J.L. Port, D.M. Libby, R.J. Korst, D.B. Flieder, C. A. Ferrara, D.F. Yankelevitz, K. Subbaramaiah, M.W. Pasmantier, A. J. Dannenberg, Celecoxib, a selective cyclo-oxygenase-2 inhibitor, enhances the response to preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer, *J. Clin. Oncol.* 21 (2003) 2645–2650, <https://doi.org/10.1200/JCO.2003.07.127>.
- [66] S.D. Solomon, J.J. McMurray, M.A. Pfeffer, J. Wittes, R. Fowler, P. Finn, W. F. Anderson, A. Zaubler, E. Hawk, M. Bertagnoli, Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention, *N. Engl. J. Med.* 352 (2005) 1071–1080.
- [67] M. Gulyas, J.S.M. Mattsson, A. Lindgren, L. Ek, K. Lamberg Lundström, A. Behndig, E. Holmberg, P. Micke, B. Bergman, S.L.C.S. Group, COX-2 expression and effects of celecoxib in addition to standard chemotherapy in advanced non-small cell lung cancer, *Acta Oncol.* 57 (2018) 244–250 (Madr).
- [68] X. Chen, C. Yu, R. Kang, D. Tang, Iron metabolism in ferroptosis, *Front. Cell Dev. Biol.* 8 (2020), 590226, <https://doi.org/10.3389/fcell.2020.590226>.
- [69] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, R. Skouta, E.M. Zaitsev, C.E. Gleason, D.N. Patel, A.J. Bauer, A.M. Cantley, W.S. Yang, B. Morrison, B.R. Stockwell, Ferroptosis: an iron-dependent form of nonapoptotic cell death, *Cell* 149 (2012) 1060–1072, <https://doi.org/10.1016/j.cell.2012.03.042>.
- [70] D. Tang, X. Chen, R. Kang, G. Kroemer, Ferroptosis: molecular mechanisms and health implications, *Cell Res.* 31 (2021) 107–125, <https://doi.org/10.1038/s41422-020-00441-1>.
- [71] S. Dolma, S.L. Lessnick, W.C. Hahn, B.R. Stockwell, Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells, *Cancer Cell* 3 (2003) 285–296, [https://doi.org/10.1016/S1535-6108\(03\)00050-3](https://doi.org/10.1016/S1535-6108(03)00050-3).
- [72] J.P. Friedmann Angeli, M. Schneider, B. Proneth, Y.Y. Tyurina, V.A. Tyurin, V. J. Hammond, N. Herbach, M. Aichler, A. Walch, E. Eggenhofer, D. Basavarajappa, O. Rådmark, S. Kobayashi, T. Seibt, H. Beck, F. Neff, I. Esposito, R. Wanke, H. Förster, O. Yefremova, M. Heinrichmeyer, G.W. Bornkamm, E.K. Geissler, S. B. Thomas, B.R. Stockwell, V.B. O'Donnell, V.E. Kagan, J.A. Schick, M. Conrad, Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice, *Nat. Cell Biol.* 16 (2014) 1180–1191, <https://doi.org/10.1038/ncb3064>.
- [73] J.Y. Lee, W.K. Kim, K.H. Bae, S.C. Lee, E.W. Lee, Lipid metabolism and ferroptosis, *Biology* 10 (2021) 184, <https://doi.org/10.3390/biology10030184>.
- [74] V.E. Kagan, G. Mao, F. Qu, J.P.F. Angeli, S. Doll, C.S. Croix, H.H. Dar, B. Liu, V. A. Tyurin, V.B. Ritov, A.A. Kapralov, A.A. Amoscato, J. Jiang, T. Anthony-muthu, D. Mohammadyani, Q. Yang, B. Proneth, J. Klein-Seetharaman, S. Watkins, I. Bahar, J. Greenberger, R.K. Mallampalli, B.R. Stockwell, Y.Y. Tyurina, M. Conrad, H. Bayir, Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis, *Nat. Chem. Biol.* 13 (2017) 81–90, <https://doi.org/10.1038/nchembio.2238>.
- [75] H. Yuan, X. Li, X. Zhang, R. Kang, D. Tang, Identification of ACSL4 as a biomarker and contributor of ferroptosis, *Biochem. Biophys. Res. Commun.* 478 (2016) 1338–1343, <https://doi.org/10.1016/j.bbrc.2016.08.124>.
- [76] S. Doll, B. Proneth, Y.Y. Tyurina, E. Panzilius, S. Kobayashi, I. Ingold, M. Irmeler, J. Beckers, M. Aichler, A. Walch, H. Prokisch, D. Trümbach, G. Mao, F. Qu, H. Bayir, J. Füllekrug, C.H. Scheel, W. Wurst, J.A. Schick, V.E. Kagan, J.P. F. Angeli, M. Conrad, ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition, *Nat. Chem. Biol.* 13 (2017) 91–98, <https://doi.org/10.1038/nchembio.2239>.
- [77] P. Ma, L. M., D. Sj, W. Ji, Dietary lipids induce ferroptosis in caenorhabditis elegans and human cancer cells, *Dev. Cell* 54 (2020) 447–454, <https://doi.org/10.1016/j.devcel.2020.06.019>, e4.
- [78] J. Li, F. Cao, H. Yin, Z. Huang, Z. Lin, N. Mao, B. Sun, G. Wang, Ferroptosis: past, present and future, *Cell Death. Dis.* 11 (2020) 1–13, <https://doi.org/10.1038/s41419-020-2298-2>.
- [79] B.T. Vo, D. Morton, S. Komaragiri, A.C. Millena, C. Leath, S.A. Khan, TGF- β effects on prostate cancer cell migration and invasion are mediated by PGE2 through activation of p13K/AKT/mTOR pathway, *Endocrinology* 154 (2013) 1768–1779, <https://doi.org/10.1210/en.2012-2074>.
- [80] Y. Xiao, Y. Gu, P. Purwaha, K. Ni, B. Law, S. Mallik, S.Y. Qian, Characterization of free radicals formed from COX-catalyzed DGLA peroxidation, *Free Radic. Biol. Med.* 50 (2011) 1163–1170, <https://doi.org/10.1016/j.freeradbiomed.2011.02.001>.
- [81] Y. Gu, Y. Xu, B. Law, S.Y. Qian, The first characterization of free radicals formed from cellular COX-catalyzed peroxidation, *Free Radic. Biol. Med.* 57 (2013) 49–60, <https://doi.org/10.1016/j.freeradbiomed.2012.12.004>.
- [82] Y. Xu, J. Qi, X. Yang, E. Wu, S.Y. Qian, Free radical derivatives formed from cyclooxygenase-catalyzed dihomog- γ -linolenic acid peroxidation can attenuate colon cancer cell growth and enhance 5-fluorouracil's cytotoxicity, *Redox. Biol.* 2 (2014) 610–618.
- [83] X. Yang, Y. Xu, T. Wang, D. Shu, P. Guo, K. Miskimins, S.Y. Qian, Inhibition of cancer migration and invasion by knocking down delta-5-desaturase in COX-2 overexpressed cancer cells, *Redox. Biol.* 11 (2017) 653–662.
- [84] Y. Xu, X. Yang, P. Zhao, Z. Yang, C. Yan, B. Guo, S.Y. Qian, Knockdown of delta-5-desaturase promotes the anti-cancer activity of dihomog- γ -linolenic acid and enhances the efficacy of chemotherapy in colon cancer cells expressing COX-2, *Free Radic. Biol. Med.* 96 (2016) 67–77, <https://doi.org/10.1016/j.freeradbiomed.2016.04.016>.
- [85] Y. Xu, X. Yang, T. Wang, L. Yang, Y.Y. He, K. Miskimins, S.Y. Qian, Knockdown delta-5-desaturase in breast cancer cells that overexpress COX-2 results in inhibition of growth, migration and invasion via a dihomog- γ -linolenic acid peroxidation dependent mechanism, *BMC Cancer* 18 (2018) 330.
- [86] X. Yang, Y. Xu, A. Brooks, B. Guo, K.W. Miskimins, S.Y. Qian, Knockdown delta-5-desaturase promotes the formation of a novel free radical byproduct from COX-catalyzed ω -6 peroxidation to induce apoptosis and sensitize pancreatic cancer cells to chemotherapy drugs, *Free Radic. Biol. Med.* 97 (2016) 342–350, <https://doi.org/10.1016/j.freeradbiomed.2016.06.028>.
- [87] K. Gao, L. Huang, Achieving efficient RNAi therapy: progress and challenges, *Acta Pharm. Sin.* B 3 (2013) 213–225, <https://doi.org/10.1016/j.apsb.2013.06.005>.
- [88] Y. Xu, X. Yang, D. Gao, L. Yang, K. Miskimins, S.Y. Qian, Dihomog- γ -linolenic acid inhibits xenograft tumor growth in mice bearing shRNA-transfected HCA-7 cells targeting delta-5-desaturase, *BMC Cancer* 18 (2018) 1268.
- [89] Y. Xu, L. Pang, H. Wang, C. Xu, H. Shah, P. Guo, D. Shu, S.Y. Qian, Specific delivery of delta-5-desaturase siRNA via RNA nanoparticles supplemented with dihomog- γ -linolenic acid for colon cancer suppression, *Redox. Biol.* 21 (2019), 101085.
- [90] D. Shu, Y. Shu, F. Haque, S. Abdelmawla, P. Guo, Thermodynamically stable RNA three-way junction for constructing multifunctional nanoparticles for delivery of therapeutics, *Nat. Nanotechnol.* 6 (2011) 658–667, <https://doi.org/10.1038/nnano.2011.105>.
- [91] M.A. Mohtar, S.E. Syafruddin, S.N. Nasir, L.T. Yew, Revisiting the roles of pro-metastatic EpCAM in cancer, *Biomolecules* 10 (2020), <https://doi.org/10.3390/biom10020255>.
- [92] G. Hoxhaj, B.D. Manning, The PI3K–AKT network at the interface of oncogenic signalling and cancer metabolism, *Nat. Rev. Cancer* 20 (2020) 74–88, <https://doi.org/10.1038/s41568-019-0216-7>.
- [93] C.H. Jung, C.B. Jun, S.H. Ro, Y.M. Kim, N.M. Otto, J. Cao, M. Kundu, D.H. Kim, ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery, *Mol. Biol. Cell* 20 (2009) 1992–2003, <https://doi.org/10.1091/mbc.e08-12-1249>.
- [94] S. Shimizu, K. Akimoto, Y. Shinmen, H. Kawashima, M. Sugano, H. Yamada, Sesamin is a potent and specific inhibitor of delta 5 desaturase in polyunsaturated fatty acid biosynthesis, *Lipids* 26 (1991) 512–516, <https://doi.org/10.1007/BF02536595>.
- [95] S. Shimizu, S. Jareonkitmongkol, H. Kawashima, K. Akimoto, H. Yamada, Inhibitory effect of curcumin on fatty acid desaturation in mortierella alpina 1S-4 and rat liver microsomes, *Lipids* 27 (1992) 509–512, <https://doi.org/10.1007/BF02536132>.
- [96] M.G. Obukowicz, A. Raz, P.D. Pyla, J.G. Rico, J.M. Wendling, P. Needleman, Identification and characterization of a novel delta6/delta5 fatty acid desaturase inhibitor as a potential anti-inflammatory agent, *Biochem. Pharmacol.* 55 (1998) 1045–1058, [https://doi.org/10.1016/s0006-2952\(97\)00665-5](https://doi.org/10.1016/s0006-2952(97)00665-5).
- [97] Z. Arshad, S. Rezapour-Firouzi, M. Ebrahimifard, A. Mosavi Jarrahi, M. Mohammadian, Association of delta-6-desaturase expression with aggressiveness of cancer, diabetes mellitus, and multiple sclerosis: a narrative review, *Asian Pac. J. Cancer Prev.* 20 (2019) 1005–1018, <https://doi.org/10.31557/APJCP.2019.20.4.1005>.
- [98] D.F. Horrobin, Fatty acid metabolism in health and disease: the role of Δ -6-desaturase, *Am. J. Clin. Nutr.* 57 (1993) 732S–737S, <https://doi.org/10.1093/ajcn/57.5.732S>.
- [99] S. Shimizu, S. Jareonkitmongkol, H. Kawashima, K. Akimoto, H. Yamada, Inhibitory effect of curcumin on fatty acid desaturation in mortierella alpina 1S-4 and rat liver microsomes, *Lipids* 27 (1992) 509–512, <https://doi.org/10.1007/BF02536132>.
- [100] S. Shimizu, K. Akimoto, Y. Shinmen, H. Kawashima, M. Sugano, H. Yamada, Sesamin is a potent and specific inhibitor of Δ 5 desaturase in polyunsaturated fatty acid biosynthesis, *Lipids* 26 (1991) 512–516, <https://doi.org/10.1007/BF02536595>.
- [101] A. Giordano, G. Tommonaro, Curcumin and cancer, *Nutrients* 11 (2019) 2376, <https://doi.org/10.3390/nu1102376>.
- [102] A.F. Majdalawieh, M. Massri, G.K. Nasrallah, A comprehensive review on the anticancer properties and mechanisms of action of sesamin, a lignan in sesame seeds (*Sesamum indicum*), *Eur. J. Pharmacol.* 815 (2017) 512–521, <https://doi.org/10.1016/j.ejphar.2017.10.020>.
- [103] X. Wang, J. Qiao, C. Zou, Y. Zhao, Y. Huang, Sesamin induces cell cycle arrest and apoptosis through p38/C-Jun N-terminal kinase mitogen-activated protein kinase pathways in human colorectal cancer cells, *Anticancer Drugs* 32 (2021) 248–256, <https://doi.org/10.1097/CAD.0000000000001031>.
- [104] T.N. Kuo, C.S. Lin, G.D. Li, C.Y. Kuo, S.H. Kao, Sesamin inhibits cervical cancer cell proliferation by promoting p53/Pten-mediated apoptosis, *Int. J. Med. Sci.* 17 (2020) 2292–2298, <https://doi.org/10.7150/ijms.48955>.
- [105] P. Kongtawelert, B. Wudtiwai, T.H. Shwe, P. Pothacharoen, T. Phitak, Inhibition of programmed death ligand 1 (PD-L1) expression in breast cancer cells by sesamin, *Int. Immunopharmacol.* 86 (2020), 106759, <https://doi.org/10.1016/j.intimp.2020.106759>.
- [106] J.M. Chen, P.Y. Chen, C.C. Lin, M.C. Hsieh, J.T. Lin, Antimetastatic effects of sesamin on human head and neck squamous cell carcinoma through regulation of matrix metalloproteinase-2, *Molecules* 25 (2020) 2248, <https://doi.org/10.3390/molecules25092248>.
- [107] M. Iqbal, M.D. Shah, S. Vun-Sang, Y. Okazaki, S. Okada, The therapeutic potential of curcumin in alleviating N-diethylnitrosamine and iron nitrilotriacetate induced renal cell tumours in mice via inhibition of oxidative stress: Implications for cancer chemoprevention, *Biomed. Pharmacother.* 139 (2021), 111636, <https://doi.org/10.1016/j.biopha.2021.111636>.
- [108] Curcumin sensitizes prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L by inhibiting nuclear factor- κ B through suppression of I κ B α phosphorylation | *Mol. Cancer Ther.*, (n.d.), <https://mct.aacrjournals.org/content/3/7/7803.long> (accessed July 29, 2021).

- [109] K.B. Harikumar, B. Sung, S.T. Tharakan, M.K. Pandey, B. Joy, S. Guha, S. Krishnan, B.B. Aggarwal, Sesamin manifests chemopreventive effects through the suppression of NF- κ B-regulated cell survival, proliferation, invasion, and angiogenic gene products, *Mol. Cancer Res.* 8 (2010) 751–761, <https://doi.org/10.1158/1541-7786.MCR-09-0565>.
- [110] H. Yashiro, S. Takagahara, Y.O. Tamura, I. Miyahisa, J. Matsui, H. Suzuki, S. Ikeda, M. Watanabe, A novel selective inhibitor of delta-5 desaturase lowers insulin resistance and reduces body weight in diet-induced obese C57BL/6J mice, *PLoS One* 11 (2016), <https://doi.org/10.1371/journal.pone.0166198>.
- [111] H. Nagase, S. Takagahara, Y. Satomi, A. Ando, K. Kubo, S. Ikeda, Effects of compound-326, a selective delta-5 desaturase inhibitor, in ApoE knockout mice with two different protocols for atherosclerosis development, *J. Pharm. Pharm. Sci.* 24 (2021) 71–83, <https://doi.org/10.18433/jpps31389>.
- [112] J. Fujimoto, R. Okamoto, N. Noguchi, R. Hara, S. Masada, T. Kawamoto, H. Nagase, Y.O. Tamura, M. Imanishi, S. Takagahara, K. Kubo, K. Tohyama, S. Ikeda, T. Andou, I. Miyahisa, J. Matsui, R. Hayashi, T. Maekawa, N. Matsunaga, Discovery of 3,5-diphenyl-4-methyl-1,3-oxazolidin-2-ones as novel, potent, and orally available Δ -5 desaturase (D5D) inhibitors, *J. Med. Chem.* 60 (2017) 8963–8981, <https://doi.org/10.1021/acs.jmedchem.7b01210>.
- [113] I. Miyahisa, H. Suzuki, A. Mizukami, Y. Tanaka, M. Ono, M.S. Hixon, J. Matsui, T-3364366 targets the desaturase domain of delta-5 desaturase with nanomolar potency and a multihour residence time, *ACS Med. Chem. Lett.* 7 (2016) 868–872, <https://doi.org/10.1021/acsmedchemlett.6b00241>.
- [114] Compound for inhibition of delta-5-desaturase (d5d) and treatment of cancer and inflammation - Patent US-2019070193-A1 - PubChem, (n.d.). <https://pubchem.ncbi.nlm.nih.gov/patent/US2019070193> (accessed January 11, 2021).
- [115] L. Pang, H. Shah, S. Qian, V. Sathish, Iminodibenzyl redirected cyclooxygenase-2 catalyzed dihomogamma-linolenic acid peroxidation pattern in lung cancer, *Free Radic. Biol. Med.* (2021), <https://doi.org/10.1016/j.freeradbiomed.2021.06.004>.
- [116] M. Sadiq, L. Pang, M. Johnson, V. Sathish, Q. Zhang, D. Wang, 2D Nanomaterial, Ti3C2 MXene-based sensor to guide lung cancer therapy and management, *Biosensors* 11 (2021), <https://doi.org/10.3390/bios11020040> (Basel).
- [117] A.P. Simopoulos, The importance of the ratio of omega-6/omega-3 essential fatty acids, *Biomed. Pharmacother.* 56 (2002) 365–379, [https://doi.org/10.1016/S0753-3322\(02\)00253-6](https://doi.org/10.1016/S0753-3322(02)00253-6).
- [118] E. Scaioli, E. Liverani, A. Belluzzi, The imbalance between n-6/n-3 polyunsaturated fatty acids and inflammatory bowel disease: a comprehensive review and future therapeutic perspectives, *Int. J. Mol. Sci.* 18 (2017) 2619, <https://doi.org/10.3390/ijms18122619>.
- [119] K. Tsuge, T. Inazumi, A. Shimamoto, Y. Sugimoto, Molecular mechanisms underlying prostaglandin E2-exacerbated inflammation and immune diseases, *Int. Immunol.* 31 (2019) 597–606, <https://doi.org/10.1093/intimm/dxz021>.
- [120] C. Yao, D. Sakata, Y. Esaki, Y. Li, T. Matsuoka, K. Kuroiwa, Y. Sugimoto, S. Narumiya, Prostaglandin E 2-EP4 signaling promotes immune inflammation through T H 1 cell differentiation and T H 17 cell expansion, *Nat. Med.* 15 (2009) 633–640, <https://doi.org/10.1038/nm.1968>.
- [121] C. Yao, T. Hirata, K. Soontrapa, X. Ma, H. Takemori, S. Narumiya, Prostaglandin E 2 promotes Th1 differentiation via synergistic amplification of IL-12 signalling by cAMP and PI3-kinase, *Nat. Commun.* 4 (2013) 1685, <https://doi.org/10.1038/ncomms2684>.
- [122] Y. Kim, J. Kim, N-6 polyunsaturated fatty acids and risk of cancer: accumulating evidence from prospective studies, *Nutrients* 12 (2020) 2523, <https://doi.org/10.3390/nu12092523>.
- [123] Y. Sakai, T. Sasahira, H. Ohmori, K. Yoshida, H. Kuniyasu, Conjugated linoleic acid reduced metastasized LL2 tumors in mouse peritoneum, *Virchows Arch.* 449 (2006) 341–347, <https://doi.org/10.1007/s00428-006-0249-7>.
- [124] N. Serma-Marquez, R. Diaz-Aragon, E. Reyes-Urbe, P. Cortes-Reynosa, E. P. Salazar, Linoleic acid induces migration and invasion through FFAR4-and PI3K/Akt-dependent pathway in MDA-MB-231 breast cancer cells, *Med. Oncol.* 34 (2017) 111.
- [125] B.K. Stowikowski, H. Drzewiecka, M. Malesza, I. Mądry, K. Sterzyńska, P. Jagodziński, The influence of conjugated linoleic acid on the expression of peroxisome proliferator-activated receptor- γ and selected apoptotic genes in non-small cell lung cancer, *Mol. Cell. Biochem.* 466 (2020) 65–82, <https://doi.org/10.1007/s11010-020-03689-8>.
- [126] A. Greenhough, H.J.M. Smartt, A.E. Moore, H.R. Roberts, A.C. Williams, C. Paraskeva, A. Kaidi, The COX-2/PGE 2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment, *Carcinogenesis* 30 (2009) 377–386, <https://doi.org/10.1093/carcin/bgp014>.
- [127] D. Wang, H. Wang, J. Brown, T. Daikoku, W. Ning, Q. Shi, A. Richmond, R. Strieter, S.K. Dey, R.N. DuBois, CXCL1 induced by prostaglandin E2 promotes angiogenesis in colorectal cancer, *J. Exp. Med.* 203 (2006) 941–951, <https://doi.org/10.1084/jem.20052124>.
- [128] P. Nandi, G.V. Girish, M. Majumder, X. Xin, E. Tutunea-Fatan, P.K. Lala, PGE2 promotes breast cancer-associated lymphangiogenesis by activation of EP4 receptor on lymphatic endothelial cells, *BMC Cancer* 17 (2017) 11, <https://doi.org/10.1186/s12885-016-3018-2>.
- [129] R. Pai, I.L. Szabo, B.A. Soreghan, S. Atay, H. Kawanaka, A.S. Tarnawski, PGE2 Stimulates VEGF expression in endothelial cells via ERK2/JNK1 signaling pathways, *Biochem. Biophys. Res. Commun.* 286 (2001) 923–928, <https://doi.org/10.1006/bbrc.2001.5494>.
- [130] S. Dada, N. Demartines, O. Dormond, mTORC2 regulates PGE2-mediated endothelial cell survival and migration, *Biochem. Biophys. Res. Commun.* 372 (2008) 875–879, <https://doi.org/10.1016/j.bbrc.2008.05.154>.
- [131] M.D. Salvado, A. Di Gennaro, L. Lindbom, B. Agerberth, J.Z. Haeggström, Cathelicidin LL-37 induces angiogenesis via PGE2-EP3 signaling in endothelial cells, *in vivo* inhibition by aspirin, *Arterioscler. Thromb. Vasc. Biol.* 33 (2013) 1965–1972, <https://doi.org/10.1161/ATVBAHA.113.301851>.
- [132] N. Obermajer, R. Muthuswamy, K. Odunsi, R.P. Edwards, P. Kalinski, PGE2-induced CXCL12 production and CXCR4 expression controls the accumulation of human MDSCs in ovarian cancer environment, *Cancer Res.* 71 (2011) 7463–7470, <https://doi.org/10.1158/0008-5472.CAN-11-2449>.
- [133] Y. Zhang, Q. Liu, M. Zhang, Y. Yu, X. Liu, X. Cao, Fas signal promotes lung cancer growth by recruiting myeloid-derived suppressor cells via cancer cell-derived PGE2, *J. Immunol.* 182 (2009) 3801–3808, <https://doi.org/10.4049/jimmunol.0801548>.
- [134] D. Che, S. Zhang, Z. Jing, L. Shang, S. Jin, F. Liu, J. Shen, Y. Li, J. Hu, Q. Meng, Y. Yu, Macrophages induce EMT to promote invasion of lung cancer cells through the IL-6-mediated COX-2/PGE2/ β -catenin signalling pathway, *Mol. Immunol.* 90 (2017) 197–210, <https://doi.org/10.1016/j.molimm.2017.06.018>.
- [135] E. Bonavita, C.P. Bromley, G. Jonsson, V.S. Pelly, S. Sahoo, K. Walwyn-Brown, S. Mensurado, A. Moieni, E. Flanagan, C.R. Bell, S.C. Chiang, C.P. Chikkanna-Gowda, N. Rogers, B. Silva-Santos, S. Jaillon, A. Mantovani, C. Reis e Sousa, N. Guerra, D.M. Davis, S. Zelenay, Antagonistic inflammatory phenotypes dictate tumor fate and response to immune checkpoint blockade, *Immunity* 53 (2020) 1215–1229, <https://doi.org/10.1016/j.immuni.2020.10.020>, e8.
- [136] M.S.G. Montani, R. Benedetti, S. Piconese, F.M. Pulcinelli, A.M. Timperio, M. A. Romeo, L. Masuelli, M. Mattei, R. Bei, G. D'Orazi, M. Cirone, PGE2 released by pancreatic cancer cells undergoing ER stress transfers the stress to DCs impairing their immune function, *Mol. Cancer Ther.* 20 (2021) 934–945, <https://doi.org/10.1158/1535-7163.MCT-20-0699>.
- [137] S. Tomić, B. Joksimović, M. Bekić, M. Vasiljević, M. Milanović, M. Čolić, D. Vučević, Prostaglandin-E2 potentiates the suppressive functions of human mononuclear myeloid-derived suppressor cells and increases their capacity to expand IL-10-producing regulatory T cell subsets, *Front. Immunol.* 0 (2019), <https://doi.org/10.3389/fimmu.2019.00475>.
- [138] J.F. Flamiatos, T.M. Beer, J.N. Graff, K.M. Eilers, W. Tian, H.S. Sekhon, M. Garzotto, Cyclooxygenase-2 (COX-2) inhibition for prostate cancer chemoprevention: double-blind randomised study of pre-prostatectomy celecoxib or placebo, *BJU Int.* 119 (2017) 709–716, <https://doi.org/10.1111/bju.13612>.
- [139] M.M. Bertagnolli, Chemoprevention of colorectal cancer with cyclooxygenase-2 inhibitors: two steps forward, one step back, *Lancet Oncol.* 8 (2007) 439–443, [https://doi.org/10.1016/S1470-2045\(07\)70139-0](https://doi.org/10.1016/S1470-2045(07)70139-0).
- [140] M.G. Obukowicz, A. Raz, P.D. Pyla, J.G. Rico, J.M. Wendling, P. Needleman, Identification and characterization of a novel Δ 6/ Δ 5 fatty acid desaturase inhibitor as a potential anti-inflammatory agent, *Biochem. Pharmacol.* 55 (1998) 1045–1058, [https://doi.org/10.1016/S0006-2952\(97\)00665-5](https://doi.org/10.1016/S0006-2952(97)00665-5).